Review Article

Electrophysiological Methods for Study of Changes in Visual Analyzer in Patients with Diabetes Mellitus

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Abstract: *The electrophysiological (EF) methods are objective methods for studying the visual analyzer function. These include electroretinography (ERG), electrooculography (EOG) and visual evoked potentials (VEPs). ERG and EOG are used for diagnosis and monitoring of a number of diseases of the retina. VEPs depend on the functional integrity of the entire optical path from the retina through the optic nerve, optic tract, the optical radiation to the visual cortex. The electrophysiological methods are widely used in studying the function of the visual analyzer in the ophthalmic and neurological practice, for objectively measuring the visual acuity and the visual field in non-cooperative patients, small children and in simulation.*
Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia. One of the late complications of DM is diabetic retinopathy (DR). It is one of the most serious complications of diabetes, often leading to blindness. Nowadays, DR includes retinal neurodegeneration and microvascular complications.
By EF studies can evaluate the function of the retina in diabetic patients in an objective manner using ERG, that reflects the EF activity of the neurons in the retina and VEPs, which indicate the electrical conductivity across the optic tract to the visual cortex.

Keywords: *Electroretinography, Visual evoked potentials, Visual analyzer, Diabetes mellitus.*

Introduction

According to the latter definition of the International Expert Committee diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia, which is a result of impaired insulin secretion, decreased insulin action, or both [2, 187].

According to Wourld Health Organization (WHO) by 2000 at least 171 million people worldwide (2.8% of the total population) suffer from DM. To date, approximately 366 million people worldwide have diabetes and this number is expected to increase. By 2030 their number will reach 522 million. The disease is present in both developed and developing countries. There is a pandemic of DM.

The symptoms of DM usually occur when blood sugar levels become extremely high or start manifestations of complications [55, 85]. According to the United Kingdom Prospective Diabetes Study (UKPDS) 25% of patients with newly discovered type 2 diabetes have retinopathy, indicating that the disease had begun years before diagnosis [118, 198, 239]. Vascular retinopathy, microaneurysms, small hemorrhages and exudates are found in 9-10% of people without diabetes [83, 216, 236]. In patients with impaired glucose tolerance (IGT), the prevalence of retinopathy is 11-12% [160, 216]. In the Hoorn Study is found a detectable correlation between retinopathy and elevated blood pressure, obesity, and high serum levels of cholesterol and triglycerides [216].

The late complications of DM can lead to serious consequences - blindness, chronic renal failure (CRF), amputation of limbs, ischemic heart disease (IHD), myocardial infarction (MI), cerebrovascular disease. Representative studies have shown that diabetics are at 15 times higher risk of blindness, and development of CRF as compared with non-diabetics as well as a development of gangrene and amputation of a lower limb. MI is 3 times more common in diabetics than in the general population [210].

Diabetic retinopathy

Diabetic retinopathy (DR) is one of the most serious complications of diabetes, often leading to blindness [9, 12, 40, 43, 54, 85, 116, 129, 185, 212, 231]. The spread of DR is proportional to the distribution of DM [115]. DR has been used to determine the levels of hyperglycemia which are the basis for the diagnosis of diabetes based on studies in which the incidence of retinopathy increases in fasting plasma glucose above 7.0 mmol/l [55, 56, 148]. DR is generally non-proliferative (NPDR) and proliferative (PDR) [109]. The pathomorphological changes occurring as a result of hyperglycemia and the formation of osmotic active sorbitol and fructose that occur in the early stages [136]. DR are expressed in damage to the small vessels - precapillary arterioles, capillaries and venules. There is endothelial proliferation of capillaries, endothelium swelling and signs of improper pericytes destruction, formation of microaneurysms. This impairs the blood-retinal barrier and increases vascular permeability, leading to edema in the macula and the whole retina and formation of hard exudates. Diabetic macular edema is a major cause of reduced vision in diabetics [155]. Excessive formation of collagen is observed, leading to thickening of the basement membrane in the walls of capillaries and subsequent narrowing of the lumen thereof. The endothelial cells begin to release an increased amount thrombocyte aggregating factors leading to increased thrombus formation, microinfarction and focal retinal ischemia. Microaneurysms considered to be an important predictor of progression of DR in newly diagnosed type 2 diabetics [126]. The capillary occlusions whose expression are the soft exudates, lead to the formation of hypoxic areas, which activates the formation of arterial-venous shunts termed intraretinal proliferation, followed by neovascularization and later fibroglial proliferation. In the macula is observed hypoxic maculopathy [193]. There are also intraretinal (punctate and spotted), subretinal and preretinal hemorrhages. It graduated with haemophthalmus and tractional retinal detachment [180]. In the Wisconsin epidemiological study of diabetic retinopathy (WESDR) the prevalence of DR in type 1 diabetes was very low (about 1%) [62, 118, 121]. In the same study [119] the prevalence of DR increased from 2% in those with diabetes duration of less than two years to 98% for duration longer than 15 years. In type 2 diabetes, the presence of DR was set at the first ophthalmological examination in 11-25% of patients, indicating that the disease begins years before diagnosis [84, 160]. 22% of newly diagnosed patients with type 2 diabetes without retinopathy at baseline, developed retinopathy after six

years in the United Kingdom Prospective Diabetic Study (UKPDS) [203]. Klein et al. [119, 120] have established retinopathy in 29% of patients with type 2 diabetes within 5 years of diagnosis. In type 1 and type 2 diabetes has been shown that HbA1c (indicator of long-term glycemic control) was strongly associated with the development of retinopathy [127, 186, 204, 205]. When type 1 diabetes was accompanied by hypertension, retinopathy could worsen [182]. Also, type 2 diabetes hypertension is associated with the development of retinopathy [160, 205]. In patients with type 2 diabetes who participated in the UKPDS was found that the strict control of blood pressure prevents worsening of DR [145]. Retinopathy in individuals with prediabetes was set at 11-12% [160, 216]. In the Hoorn study was established 13.6% DR in patients with prediabetes with 9 year duration. Risk factors associated with retinopathy are hyperglycemia, hypertension, and abdominal obesity, dyslipidemia [217]. Few researches have been found about the incidence of retinopathy in patients with prediabetes.

From a functional standpoint the retina is vascularized neuronal tissue. The retinal blood supply is carried out from choroidal vessels and retinal vessels, located in the inner layers of the retina and mainly in the ganglion cell layer (GCL) and is logical that the occurrence of vascular changes have early effect on neurons, particularly sensitive to hypoxia. Today DR includes retinal neurodegeneration and microvascular complications [11]. Back in 1962, Bloodworth [27] described the DR as a complex degenerative disease of all elements of the retina. Nowadays, there is a great emphasis on neurodegenerative part of the DR [11, 19, 30, 133]. According to Algan et al. [3] the optical neuropathy in diabetes is 4 types: axial, or this is the classic optic neuropathy, anterior ischemic optic neuropathy (acute ischemia, which depends on the number of nerve fibers affected), acute papilledema – manifests itself in young diabetics type 1 and can be asymptomatic due to capillaropathy. The fourth type is the final stage of the first three – optic atrophy. According to Nedzvetskaia and Chumak [163] damage to the optic nerve occurs more frequently in patients with PDR and less frequently in prePDR. Defects in color vision and decreased sensitivity were reported in diabetic patients with no or minimal retinopathy [18, 50, 68, 73]. Reduced sensitivity is observed in patients with prediabetes [52, 66, 190].

Electrophysiological methods fot study the visual analyzer

The electrophysiological (EF) methods are objective methods for studying the visual analyzer function. These include electroretinography (ERG), electrooculography (EOG) and visual evoked potentials (VEPs). ERG and EOG are used for diagnosis and monitoring of a number of diseases of the retina.VEPs depend on the functional integrity of the entire optical path from the retina through the optic nerve, optic tract, the optical radiation to the visual cortex. EF methods are widely used in studying the function of the visual analyzer in a number of diseases in the ophthalmic and neurological practice for objectively measuring the visual acuity (VA) and the visual field in non-cooperative patients, small children and in simulation [58, 170, 224, 229].

Electroretinogram

The electroretinogram (ERG) is an objective EF diagnostic test which measures the electrical activity generated by the neural and non-neural cells of the retina in response to light stimulation. The electrical response is a result of retinal potential generated by light-induced changes in the flow of intraretinal ions, preferably sodium and potassium. Most often ERG is prepared using electrodes embedded in a corneal contact lens, which measure the total retinal electrical activity on the surface of the cornea [58]. The International Society for Clinical Electrophysiology of Vision (ISCEV) established minimum standards for ERG in 1989, which are periodically

updated. ERG can provide important information for diagnosing and monitoring the progression of various diseases of the retina. ERG is used in studying the function of the visual analyzer, for objectively measuring the VA in non-cooperative patients, small children and in simulation [58, 229].

ERG represents an analog curve containing the following components (Fig. 1):

- *a-wave*: an initial corneal-negative deflection received by the rods and cones of the outer photoreceptor layer of the retina.
  This wave reflects the hyperpolarization of the photoreceptors due to the closing of the sodium ion channels in the outer-segment membrane. The light absorption activates rhodopsin to activate transducin, which is a G-protein. This leads to activation of the cyclic guanosine monophosphate phosphodiesterase (cGMP-PDE), which leads to reduction of the level of cGMP in the photoreceptor. This leads to the closing of the sodium ion channels, resulting in a reduced flow of sodium ions into the cell or to its hyperpolarization. A-wave reflects the general physiological condition of the photoreceptors in the outer retina. The amplitude (A) of a-wave is measured from midline to the wavelength peak [58, 71].
- *b-wave*: corneal positive deviation derived from the inner layers of the retina, mainly Muller cells and bipolar cells.
  The photoreceptor cells hyperpolarization results in a reduction of the amount of the released neurotransmitter, which subsequently leads to hyperpolarization of the postsynaptic bipolar cells. Depolarization of the bipolar cells increases the level of extracellular potassium, leading to generation of intraretinal potential. It depolarizes the radially oriented Muller cells and generates corneal positive deviation [58]. The b-wave reflects the condition of cells of the inner layers of the retina, including bipolar cells and Muller cells [152]. The amplitude of b-wave is generally measured from the peak of a-wave to the peak of b-wave. This wave is the most frequently used component of ERG in the clinical and experimental analysis of human retinal function.
- *c-wave*: derived from the retinal pigment epithelium (RPE) and photoreceptors.
  C-wave reflects the resultant change in transepithelial potential due to the hyperpolarization in the apical membrane of the cells of RPE and hyperpolarization of the distal portion of Muller cells [141]. C-wave normally reaches its peak within 2 to 10 seconds of light stimulus, depending on the intensity and the duration of light. Therefore, the response is generated for a few seconds, it is susceptible to the electrode drift influences, eye movements and blinking. That, and the fact that c-wave is very variable in shape and A in healthy subjects, limited the clinical use of measurements of c-wave [58].

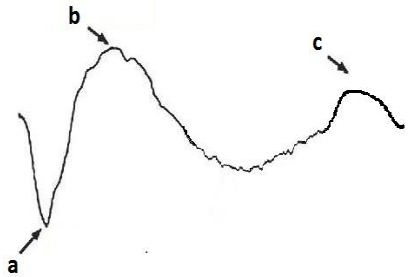

Fig. 1 Normal ERG configuration

The most commonly measured parameters in electrophysiology are: amplitude of the individual waves and latency.

Latency (L) or implicit time (IT) or peak latency (PL) is the time from the beginning of the light stimulus to the peak of the b-wave (Fig. 2).

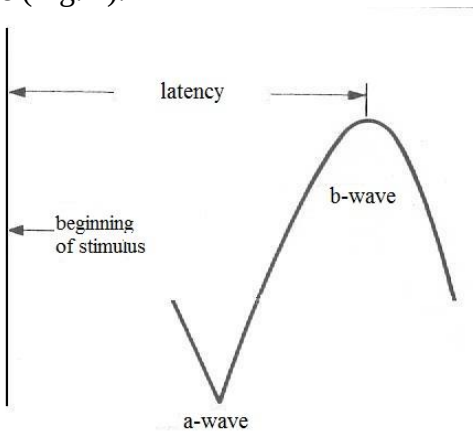

Fig. 2 Measurement of latency

Amplitudes of the responses are measured in microvolts (μV), and L in milliseconds (ms) [149] (Fig. 3).

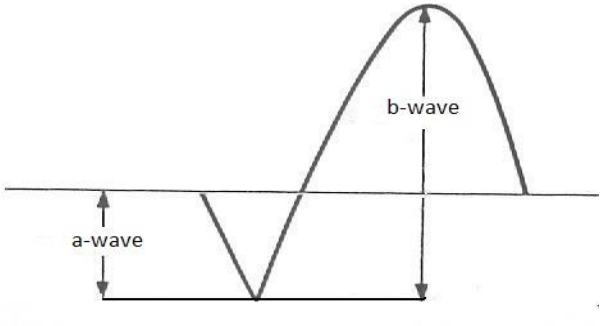

Fig. 3 Measurement of amplitudes

In healthy subjects the A and the L of a-wave are as follows: A = 279 ± 46.4 μV and L = 20.4 ± 0.8 ms, while of b-wave – A = 547 ± 103.3 μV and L = 43.11 ± 3.5 ms [228].

According to the type of A we can orient for the extent of the retinal involvement. A slight drop in shows initial functional changes; a great reduction of A indicate an appreciable affect on the retinal function and unregistered wave shows irreversible retinal changes. Under certain conditions, such as acute hypoxia, intoxication or sympathetic ophthalmia is observed higher than normal A, indicating irritation of the retina and violation of conduction inhibitory fibers [58].

Moreover the wave A, an important diagnostic value is the b/a ratio, which normally is 2:1. As a rule A of b-wave is twice the size of A of a-wave. If this ratio is less we have affected the inner layers of the retina. It is believed that the reduction of this ratio indicates the degree of retinal ischemia and can serve as a prognostic factor for the visual function restoration [58].

Types of electrodes

Different shapes and sizes of corneal contact electrodes, bearing the names of their creators, are in use, also surface electrodes [58, 148]:

- Burian-Allen electrode (commonly used for flash ERG) – lenses with variable dimensions, consisting of a stainless steel ring surrounding the central part of polymethyl methacrylate (PMMA).
- Dawson-Trick-Litzkow electrode – thread electrode consisting of individual fibers of a special material (Mylar), impregnated with silver.
- ERG-Jet electrode – disposable plastic lens with gold periphery.
- Mylar electrode – aluminized or gold- coated Mylar fiber.
- Cotton-Wick electrode – modification of Burian-Allen electrode that uses a cotton swab to minimize light-induced artifacts.
- Hawlina-Konec loop-electrode – teflon insulated thin metal wire (silver, gold, platinum) with three central holes 3 mm in length, which is placed in the lower conjunctival sac.
- Skin electrode – can be used as a substitute of corneal electrodes by placing on the skin near the infraorbital lower eyelid. Due to low amplitudes and variable responses, this electrode is primarily used for screening or in children who do not tolerate corneal electrodes (Fig. 4).

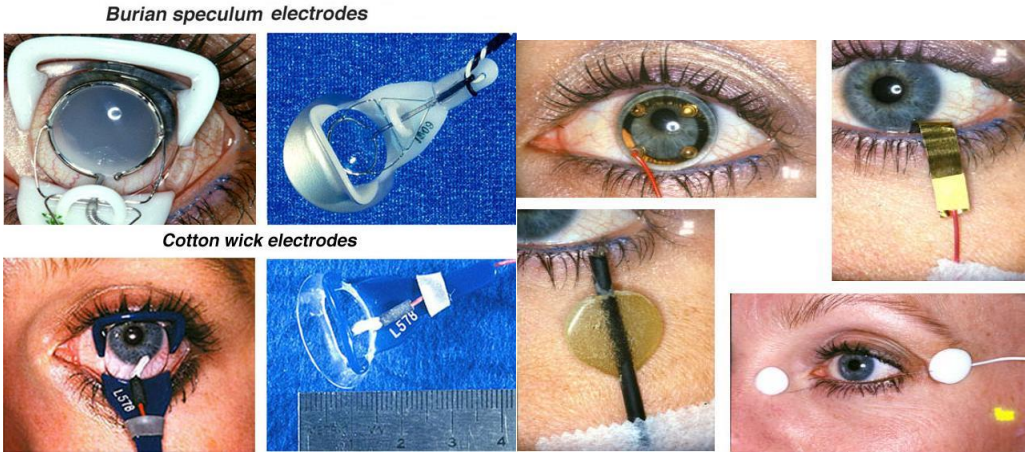

Fig. 4 Types of electrodes
(adapted from http://vetprofiles.tufts.edu/faculty/carlos-m-gradil)

Factors influencing ERG

- Duration of stimulus – in short stimuli a reciprocal relationship exists between the duration of stimulus and the intensity, so if the intensity is kept constant, prolonged stimulus will cause greater amplitude response. Muller-Limmroth [159] found that if the stimulus duration is more than 20 ms all the stimuli are equal. The ISCEV standard recommends maximum stimulus duration of 5 ms [58, 149].
- Area illuminated retina – in full field ERG (ffERG) is obtained homogeneous diffuse retinal response. The surface of the retina sprays the stimulus in that way so the entire retina is affected. If the light focuses only on a small area, is obtained focal ERG from the illuminated retinal area only (focal ERG) [58]. In multifocal ERG (mfERG) is obtained aggregate response of many such areas. The area of the affected retina also affects the A of the response. Schuurmans et al. [196] investigated in rabbits the influence of the area of photocoagulated

retina on the A of ERG and concluded that at up to 20 degrees photocoagulation of the retinal area there is no change in the A, between 20-60 degrees there is a reduction in A proportional to the area photocoagulated retina.

- Interval between stimuli – adequate interval varies depending on the duration and intensity of the stimulus. When measured response of isolated dark-adapted rods, recommended minimum interval between stimuli is 2 seconds. Interval of at least 10 seconds is recommended for measuring of dark-adapted combined response of rods and cones. In light adapted eyes interval of 0.5 sec. is recommended [58].
- Pupil size – the illumination of the retina is proportional to the pupil size [58].
- Availability of drugs in blood circulation – some vasodilators, such as papaverine and acetylcholine influence ERG amplitude, increase the amplitude of b-wave [86]. Hyperventilation influences ERG in the same way [58].
- Development of the retina – in infants observed decreased A and extended L, which are developing fast in the first months to reach adult values at different ages according to different authors – 2 to 5-6 months to 1 year [65, 149, 226].
- Transparency of the ocular media – opaque ocular media acts as a filter, which reduces the amount of light reaching the retina – the result is reduced A and extended L [58].
- Age, gender and refractive errors – the depending on age is linear. All authors believe that with age becomes reduction of A of b-wave and extending of L. In women this happens clearly at age 40-49, probably hormone conditioned. The decrease in amplitude begins after the third decade and up to 69-70 years there is a decline to 50% compared with young adults 15-25 years [58]. Concerning gender, some authors believe that in all ages statistically significant increased A of b-wave have the women [26, 226]. Myopia more than 6 diopters reduces the amplitude of b-wave – probably this is related to the increased axial length and chorioretinal damages at those eyes [175].
- Anesthesia – affects different the A of b-wave according to the different anesthetics. In most drugs A of ERG depends on the level of anesthesia [58]. Padmos and van Norren [174] found prolongation of cone response to anesthesia with halothane, it was also observed using chloroform and diethylether.
- Circadian rhythms – it was established a difference in the A of b-wave up to 13% without influence on A of a-wave – the lower is the amplitude in 6 h. morning and the highest at 12 h at noon. It shows a good correlation with the circadian rhythm of dopamine beta-hydroxylase [58].
- The conditions under which research is carried out, such as duration of dark or light adaptation, intensity, duration, frequency and wavelength (color) of the light stimulus, viewing angle, electrodes position also affect the results, especially on the wave amplitudes [149].

ERG-techniques

The functional response of rods and cones can be divided using different ERG-techniques [149].

Full-field ERG (ff-ERG is EF method for objectively measuring the overall function of the retina, isolated general function of cones and isolated general function of rods. The first electroretinograph recordings were made in frog by Holmgren in 1865 [95]. The technique is based on registration of the overall potentials generated by the retinal cells after stimulation with light. To obtain the best sensitivity of photoreceptors, the retina is dark-adapted for 30-45 minutes

before light stimulation. This is the time required to perform a chemical process to restore photopigments. The entire retina is illuminated by light produced by Ganzfeld-field and bipolar electrode-contact lens that detects at the cornea surface the electrical activity generated by the retina [139, 149].

Ff-ERG measures the activity from the entire retina and is useful in the detection of diseases with generalized retinal dysfunction such as pigmented retinitis, hereditary photoreceptor dystrophies, Leber atrophy, toxic retinopathies and others [25, 60, 90, 147, 161, 183, 203, 211, 229]. After the family history and clinical examination, ERG is the next test for retinal dystrophies differentiation.

According to ISCEV standard ERG consists of at least 7 different tests [149].

Scotopic ERG (dark adapted eyes and weak light stimulation) combined ERG (dark-adapted eye and strong light stimulation) oscillator potentials, photopic ERG (light-adapted eyes with a strong light stimulation) and 30 Hz flicker-ERG (fast repetitive stimuli).

Scotopic (rod) response is obtained after dark adaptation for a minimum of 20 minutes according to ISCEV-standard, followed by short-wave stimulus as a single flash or 10 Hz flicker. Although the response has rod and cone component, the rod component is dominant and is the major factor of shaping the potential. It is believed that after 7-minute dark adaptation the bioelectrical activity of the rods began prevails. They respond better in low stimulus intensity – white or blue light [58].

Photopic (cone) response – as rods cannot vibrate with stimulus with a frequency greater than 20 Hz, the cone function is measured mainly after light adaptation for at least 10 minutes and a single flash stimulus (wavelength more than 680 nm) or 30 Hz flicker stimulus. The cones react better in bright stimulus – white or red. Photopic responses lead to small b-wave A with short latency (30-32 ms). The scotopic (rod) conditions cause much larger b-wave A with a long latency (60 ms) [149].

30 Hz flicker – a kind of photopic response of cones also with a stimulus frequency of 30 per second [149].

Oscillatory potentials (OPs) were first described in 1954 by Cobb and Morton [42], subsequently named by Yonemura [234]. They have a high frequency of about 100 to 160 Hz low-amplitude waves. Found both after scotopic and photopic adaptation. There are suggestions that the OPs are generated by amakrine cells in the inner retina [42, 47, 114, 222]. Tzekov and Arden [215] back in the 90s stressed the importance of OPs for the prediction of progression of NPDR to a vision-threatening PDR. According to some authors OPs were considered the most indicative EF test in DR [42]. These waves seem to reflect the activity of the negative feedback exerted by the amakrine cells to the bipolar and ganglion cells. The OPs are excellent marker for trophic disorders of the retina and are therefore often altered in patients with diabetes, even in the preclinical stage of retinopathy [31].

The focal ERG (fERG) is also known as foveal ERG. It is mostly used to measure the functional integrity of the fovea therefore provides information on macular diseases. Various techniques are

described in the literature for recording fERG. Different sizes of the field, ranging from 3° to 18° and different light frequencies were used in different methods, but all were faced with the challenge of the limited amount of light illuminating a small area of the retina. FERG is useful for assessing the macular function in age-related macular degeneration (AMD), but requires good patient fixation [58, 180, 224].

The multifocal ERG test (mfERG) was introduced by Sutter and Tran in 1992 [207]. This is a relatively new technique that allows local ERG-responses to be recorded simultaneously from many regions of the retina. The stimulating patterns consisting of hexagons (61 or 103 number) are projecting on a screen. The central hexagons are smaller than those in the periphery. The model stimulates the retina to 20-30° on both sides of the fixation point, such as hexagons alternating change from black to white and vice versa in a predetermined sequence, termed m-sequence. The resulting waveforms are similar to those of ffERG: initial negative deflection (N1 or a-wave), followed by a positive deviation (P1 or b-wave), and a second negative deflection (N2 or C-wave). The bipolar electrode is corneal contact lens which registers the retinal respond. The fixation is monitored by infrared fundus camera. The signals are processed using a mathematical system that can analyze the response of each hexagon separately. The results are shown as a summary diagram of the different local responses. The mathematical algorithm allows averaging groups of answers from successive rings from the center to the periphery, represented as group averages. The third way to present the results in topographic 3D format that shows the overall signal strength per unit area of the retina [90, 99, 101, 139, 142].

It is believed that the answers in mfERG originate from the cones, as it is proven that there is a close relation in the generation and the waveform of mfERG, on one hand, and the ff-ERG cone response on the other [102]. So as in ff-ERG, the A of the responses are measured in μV and the L in ms. MfERG is useful for detection of localized abnormalities in the retina as well as changes in the macula. Most assays of mfERG are based on the approximate mathematical calculation of A of b-wave [97]. L sometimes better describes the progression of the retinal diseases [220].

Pattern ERG (PERG) is a retinal biopotential evoked by a contrast-reversing pattern from black to white and back projected on a screen at a constant illumination not less than 80 cd/m^2, central fixation. Permanent lighting is achieved with the classic cathode stimulator. The pattern is composed of checkerboard with maximum contrast between black and white close to 100% and not less than 80%, which may be of different sizes in the various assays. Standard width of the individual check is 0.8° (± 0.2°) in stimulating field of 30° – peripheral stimulation, and 0.25° – at stimulating field of 15° – central stimulation. More limited use has the wider field of 30°. PERG not require scotopic conditions, but they must be the same in all studies. The standard rate of reversion is 2.0 ± 0.4 Hz, which corresponds to 4.0 ± 0.8 reversals per second (rps), which is the correct term. At a reversion frequency of more than 10 rps is generated a "steady-state PERG", which is very rarely used, since in such frequency is very difficult to measure the individual components [88]. The standard recommended rate of reversion is 16 rps (8 Hz) ± 20% for "steady-state PERG" [16, 58].

The generated signal passes through amplifier with a minimum input impedance of 10 MΩ. The recording frequency of the amplifier should range from 1 to 100 Hz. The amplifiers must be electrically isolated and meet the current safety standards. Because of the small A of PERG is necessary signal averaging. The minimum of 100 artefact-free sweeps should be averaged for a

standard PERG. The analysis period (sweep time) should be 150 ms or greater, with 4 rps stimulation rate and 250 ms between reversals. The system should be equipped with automatic rejection of artifacts with amplitude ±100 μV. A minimum sampling rate of 1000 Hz is recommended. The amplifiers must return rapidly to its original position after suppression of the artefact signals. At least two trials for each stimulus condition should be obtained to confirm reproducibility [16, 58].

The patient should be seated comfortably at a distance of 50-150 cm from the monitor, with stable head position. It is not required pupil dilation to obtain maximum retinal image quality. For the same reason patient should wear the appropriate optical correction for the test distance. Binocular testing is recommended as it is considered to be more stable and reduces the time of testing. Monocular stimulation is used when obtaining PERG and pattern visual evoked potentials (PVEPs) simultaneously, as well as in strabismus [16].

PERG are small signals, usually around 2-8 μV across the population, making the recording of PERG technically more difficult than the standard flash ERG [16].

According to the ISCEV standard PERG is a transient response, which is completed before the next contrast reversal. Transient PERG allows separation of its individual components. At low temporal frequency (< 6 rps), equivalent to < 3 Hz, transient PERG is obtained. PERG waveform in normal subjects usually consists of a small initial negative component with L approximately 35 ms (N35), followed by a much larger positive component (P50) about 45-60 ms, followed by a large negative component of 90-100 ms (N95) [16]. According to Fiorentini et al. [57], PERG is generated by the retinal ganglion cells (RGCs) activity. The most commonly measured is P50, which is very similar to the b-wave. Is debatable which one component shows the activity of ganglion cells but nowadays is accepted that N95 derives from the ganglion cells and P50 is generated mainly from the ganglion cells, but also distally, it is not established exactly where [88]. The amplitudes are measured standardly from peak to peak. In cases where N35 is poorly defined, the amplitude of P50 is measured from the average baseline. The latency is measured standardly as other types ERG [16]. According to Fishman et al. [58] A of P50 is between 2.5 and 5.0 μV, and A of N95 is 3.5-6.5 μV (Fig. 5).

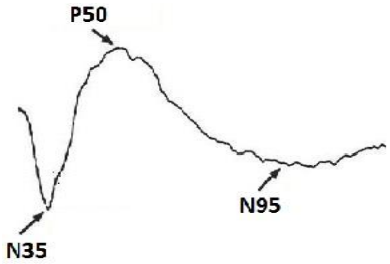

Fig. 5 Components of PERG

According to the ISCEV standard there are no standard international reference ranges for PERG measurements. Each laboratory must establish normal values for its equipment and population. We have to take into account the mentioned factors affecting ERG [16].

The using recording electrodes are standard, just like in the other types of ERG, it is better to avoid the corneal contact lens electrodes. Suitable are the fiber, foil and loop electrodes that are

placed in contact with the bulb near the medial canthus of the lower eyelid, taking care not to fall into the fornix, which would reduce the A of PERG. Blinking and eye movements should be avoided. Skin electrodes are not suitable due to the above mentioned reasons. The reference electrode is best to be placed on the skin near the lateral canthus of the tested eye. Putting it on the forehead, ear or on the mastoid is permitted, but must be careful about additional cortical potentials or any from the fellow eye. The grounding electrode is most often placed on the forehead, but other locations are acceptable also. Its location does not affect the standard PERG. The impedance between the recording and the ground electrode must be less than 5 KΩ [16].

ERG in ophthalmic and ophthalmoneurology diseases

PERG derives largely from the ganglion cells induced by the photoreceptors and the corresponding retinal cells [181]. As PERG, unlike flashERG, is a local response of the light illuminated area it can be used as a sensitive indicator of macular dysfunction and affects the integrity of the three neurons in the retina - photoreceptors, bipolar and ganglion cells [94, 189]. Clinically PERG can be used in patients with abnormal PVEPs in order to establish whether there is involvement of the central retina, which helps to differentiate if the retina or the optic nerve is a cause of the abnormal PVEPs. Even relatively small delay of PVEPs is associated with a significant reduction of P50 in PERG in the presence of macular dysfunction. Unindicated PERG or significant reduction of A, which are not associated with shortening of the L of P50, is indicative of macular dysfunction. Contrast to this, PERG may be normal in optic nerve diseases, or may indicate a reduction of A of N95, almost constantly occurring in primary affected ganglion cells [90]. PERG can be used for detection and monitoring of the RGCs dysfunction caused by diseases such as glaucoma, optic neuropathy, DM. Thus PERG has clinical value in neurological and ophthalmic practice [16]. According to Walsh [224] PERG is a sensitive indicator of the occurrence of DR, and for the occurrence of early glaucomatous changes in the retina.

Boughman and Fishman [28] studied an extended family with pigmented retinitis and found that depending on the type of inheritance and age, the changes in ERG were from extended L and reduced A to unregistered ERG, as in none of the representatives of the family was registered normal potential. In the initial stages are changed the scotopic responses only, but in the latter stages the photopic responses are also affected. There are numerous studies on hereditary rods and cones dystrophies, Stargard disease, Leber amaurosis, glaucoma, AMD, branch retinal vein oclusion [39, 168, 169, 183, 206, 237]. ERG, along with EOG are the methods by which the predominant involvement of rods or cones is defined.

ERG is investigated in retinal detachment. In general, the amplitude of ERG b-wave corresponds to the retinal detachment area although the detached retina can function for a certain time [98].

Taking of certain drugs in high doses or for a long period may lead to degeneration of the retina with pigment changes. These are thioridazine, chlorpromazine and chloroquine and hydroxychloroquine. The effect of the toxic drugs can be quantified by EF studies. Which type of ERG should be obtained depends on the mechanism and predilection area of damage in the retina. Creel et al. [47] investigated the effect of ethambutol on ERG and VEPs and found that there were changes in the latencies and A of both studies, which showed that the drug not only affected the optic nerve, but the retina also. Topiramate is also toxic to the retina, except that it causes a change in the refraction and the anterior chamber angle. ERG studies that reach electronegative wave had described Tsui et al. [213]. Chloroquine retinopathy manifests itself

initially as maculopathy. FERG may become abnormal in these cases. For detection of chloroquine toxicity American Academy of Ophthalmology recommends fundobiomicroscopy, computer perimetry (field to 10°), and at least one objective test: mfERG, study of autofluorescence, optical coherence tomography (OCT) [140]. In contrast, Amsler test, study of color vision, fluorescein angiography, ffERG and EOG are not considered informative [46, 151]. MfERG better reflects quantitatively the toxicity of the retina than ffERG.

Systemic metabolic disorders also have an impact on the retina physiology. Liver and kidney diseases and drugs that damage these organs usually reduce the ERG b-wave amplitudes [147].

Vitamin A deficiency also leads to a reduction of A of b-wave. In this case the cone-response is much more conserved than that of the rods. After several months of receiving vitamin A, the amplitudes recover [147]. This is probably due to the fact that the metabolism of cones is much faster than rods and the cone pigment is recovering much faster [5, 191, 209].

Holm et al. [96, 97] performed OCT and mfERG in patients with diabetic maculopathy and retinal detachment and found that retinal function was negatively correlated with the retina thickness and the presence of hard exudates in diabetic patients. A reduced A and a prolonged L correlate with the macular thickness. When the central macula thickness exceeds 300 μm the reduced A and the extended L are more pronounced. The eyes with hard exudates had extended L compared with those without hard exudates, although no differences in the macular thickness. The hard exudates extend the L even if they are far from the center of the fovea. The nasal macular part showed lower amplitude and prolonged L as compared to the temporal [178]. After laser treatment detected an increase in the mfERG amplitude, decreased macular thickness and absence of hard exudates. In long standing retinal detachment, the mfERG amplitude is greatly reduced or absent, but after surgery the A is recovering, although lower. Leozappa et al. [131] investigated ERG as a prognostic factor before and after vitrectomy in patients with diabetic macular edema, and Karacorlu et al. [113] before and after administration of triamcimolone acetonide in patients with the same diagnosis. Lang et al. [128] studied the toxicity of triamcimolone acetonide on human retina by ERG and concluded that its intravitreal administration did not change the EF parameters. For control serves the fellow eye.

Holder et al. [93] used the results of ffERG and PERG as an objective criterion for initiating and monitoring therapy in Birdshot retinopathy. They found EF changes during the initial asymptomatic stages and almost completely restored EF parameters in the course of therapy, indicating recovery of the retinal function and possibly stopping treatment. The earliest changes suggested a possible initial dysfunction of the inner retina with consequent further damage of the outer layers. Similar changes found and Vitale et al. [219].

Ambrosio et al. [7] found that by mfERG could predict the reduction in VA in patients with early-stage AMD. Herbik et al. [89] reported the same study, but added mfVEPs. Luo et al. [135] studied simultaneously ERG and VEPs in patients with macular diseases and concluded that exudative AMD, Stargardt disease, central serous retinopathy (RCS) and idiopathic macular hole showed more abnormalities compared with atrophic AMD and idiopathic epiretinal membrane with traction syndrome. ERG was more abnormal compared to VEPs.

Noma et al. [168] investigated ERG and the vascular endothelial growth factors (VEGF) in patients with branch retinal vein occlusion and found a correlation between the reduction of A and the extension of L of ERG, and the amount of VEGF, which could be used as an indicator of high risk patients for developing neovascularization. Moschos et al. [157, 158] studied mfERG and OCT before and after administration of anti-VEGF and triamcimolone acetonide in patients with vein occlusion as indicators of morphological and functional result. Georgiadou et al. [67] studied patients with macular edema and uveitis by mfERG and OCT and found that after therapy there was not always correlation between the reduced macular thickness, mfERG and VA – in many cases, despite the good anatomic result, no significant improvement in mfERG and VA occurred.

Many authors investigated mfERG and PERG before and after administration of anti-VEGF drugs in patients with neovascular membranes in AMD and established a significant improvement in A and L of mfERG after treatment, indicating that EF methods could be used as an indicator of improved retinal function and timing for the next application of the drug [36, 156, 171, 178, 240]. Others performed mfERG and PERG in patients with diabetes and macular edema and established improvement in retinal function after antiVEGF drugs or lasercoagulation [53, 134, 173].

According to Holder [90] PERG are abnormal in approximately 40% of patients with demyelination of the optic nerve, but in 85% of these patients the abnormalities is limited to components N95, as a result of retrograde degeneration of RGCs [91]. A small percentage of patients showed involvement of P50, but this reduction of the amplitude of P50 could be accompanied by a shortening of L of P50.

In ischemic optic neuropathy (ION) can be obtained reduction in A of N95, but P50 is more often affected in ION than in demyelination process, perhaps reflecting the more common vascular dysfunction anterior of the RGCs [6, 91, 92].

In optic nerve compression most frequently in pituitary gland tumors abnormal PERG can also occur as a result of retrograde degeneration of RGCs. Some authors believe that PERG may be a useful prognostic indicator for postoperative visual result in pituitary tumors [29, 192]. This assumption is confirmed by Parmar et al. [179] – the abnormal preoperative PERG correlates with the lack of postoperative recovery.

Electrooculography

The electrooculography (EOG) was popularized in the clinical practice by Arden et al. [13]. In this method potentials generated by eye movements are recorded by placing electrodes on the skin on both sides of the eyes – reference and active electrodes. The patient is dark adapted for 15 minutes, then in photopic conditions in every 60-second interval, are recorded electrical potentials as eyes make saccadic movements to 30 angular degrees. It is recorded for 10 minutes. In healthy eyes A of the potentials are lowest during the dark phase and subsequently increases and reach a peak during the photopic phase. Potentials recorded during the EOG are used for calculating the Arden ratio. It is obtained by dividing the peak A in photopic conditions, to the peak amplitude at dark adaptation. The Arden ratio may change depending on the methodology, including the duration of adaptation, pupil size and intensity of light. According to the ISCEV standard most often the lowest value of Arden ratio is about 1.8 in normal subjects [58, 140, 224].

EOG produces results that reflect the function of RPE. Therefore, EOG is a useful method for assessing and monitoring the RPE function in retina diseases such as pigmented retinitis or study of drug toxicity [75].

Visual evoked potentials

Visual evoked potentials are objective EF method that provides important diagnostic information about the integrity of the entire visual system. VEPs are visually induced electrophysiological signals derived from the EEG activity in the visual cortex recorded on the proper scalp. As the macula has greater representation in the visual cortex activation, most of the pulses are received from the center of the visual field. VEPs depend on the functional integrity of the entire optical pathway from the retina, through the optic nerve, optic tract, optic radiation to the visual cortex. They are used in a number of diseases in the ophthalmic and neurological practice and for an objective examination of VA and visual field in young children and aggravation [58, 170, 223].

The waveform of VEPs depends on the temporal frequency of the stimulus. In high-frequency stimulation the waveform becomes approximately sinusoidal and is termed "steady-state VEPs". In low-frequency stimulation the waveform consists of separate deflections and is termed transient VEP. All ISCEV standard VEPs are transient. The standard VEPs protocols are defined for a single-channel recording with midline occipital active electrode. These protocols are designed to assess a prechiasmal damage. If chiasmal or retrochiasmal disease is suspected, a three-channel montage, using additional active electrodes located on specific spots laterally on the scalp is recommended in addition to the basic standard tests – multichannel recordings [58, 170].

There are standardized three types of VEPs: PVEPs, PVEPs onset/offset and flashVEPs.

The standard pattern reversal VEPs (PVEPs) stimulus is a high contrast (over 80%) black and white checkerboard with a large check size 1° (60 min of arc) – for peripheral stimulation and a small one 0.25° (15 minutes) – for foveolar stimulation [58]. The number of black and white checks must be equal. The reversal rate should be 2 rps, i.e. 2 reversals per second, which corresponds to 1 Hz. The mean luminance of the checkerboard should be at least 50 cd/m^2, constant over time, and at all points on the screen. Since it is difficult to achieve in practice the admissible accepted difference center/periphery is up to 30%. Fixation point should be on the middle of the screen, the distance to the screen is usually from 50-150 cm. There are not special requirements for the room illumination but it should be the same in all researches and not brighter than the stimulus [170].

PVEPs onset/offset stimulus has the same parameters, but the checkerboard pattern is abruptly exchanged with a diffuse gray background. The duration of the stimulus should be 200 ms, followed by 400 ms gray screen [170].

The flashVEPs should be elicited by a brief flash that subtends a visual field of at least 20°, presented in a dimly illuminated room. The flashVEPs are much more variable than PVEPs across subjects, but are quite similar between eyes of an individual subject. They are suitable for children and not very cooperative patients. The strength of the flash stimulus should be 3 cd/m^2 (photopic candelas seconds per meter sq.) [58, 82, 170].

The PVEPs are the preferred stimulus in most clinical trials. They are less variable in waveform and timing than the other VEPs. PVEPs onset/offset are best suited for detecting simulation and in patients with nystagmus. FlashVEPs are useful in bad patient cooperation, poor vision and media opacities. It is believed that in VA under 0.1 is more appropriate to use flashVEPs [170].

Skin electrodes are recommended. The skin should be prepared by cleaning and a suitable contact paste or gel used, which provide good electrical conduction [224]. The electrode impedances should be less than 5 KΩ, measured between 10 and 100 Hz, and to reduce electrical interference, they must not differ by more than 20% between electrode sites. The electrodes position on the scalp should be according to the International 10/20 system [8]. The anterior/posterior midline measurements are based on the distance between the nasion-inion on the vertex. The active electrode is placed on the scalp over the visual cortex at Oz, the reference electrode at Fz. The ground electrode should be placed on the forehead, vertex, or mastoid, the ear and connected to the ground [170]. The placement of the active electrode at Oz is intended to assess a prechiasmal damage, if we want to research the chiasmal and retrochiasmal function we should use additional electrodes located at specific locations laterally on the scalp – O1 and O2 (Fig. 6).

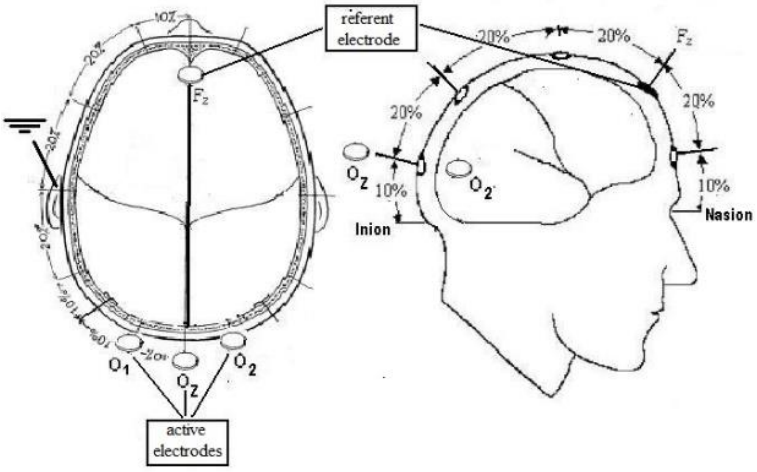

Fig. 6 Electrode positions on the scalp

According to some researchers it is enough to record PRVEPs on the midline occipital location with a stimulus frequency of 1-2 Hz and size of the checks 30' [193]. Other acceptable electrodes positions are: on the occipital midline (5 cm above the inion-a), as well as placement of the electrodes on the right and left occipital scalp (5 cm laterally from Oz) and at the frontal midline (12cm above the nasion) [170].

As a result of the stimulation there is obtained a waveform with 3 peaks – basic components of PRVEPs – N75, P100, N145 (approximately at the 75th, 100th and 145th ms in healthy subjects) [170] (Fig. 7).

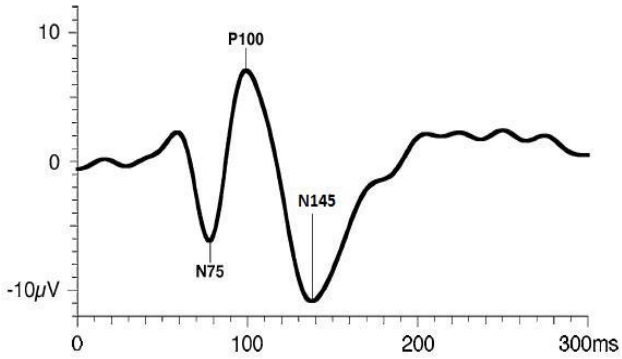

Fig. 7 Normal configuration of PRVEPs

Amplification of the input signal by 20000-50000 times is appropriate, the input impedance of the amplifiers must be at least 100 MΩ and the common mode rejection ratio should exceed 120 dB. The amplifiers must be electrically isolated from the patient and meet the current safety standards. The analogue signal should be digitized at a minimum sample rate of 500 samples per second per channel with a minimum resolution of 12 bits. Automatic artifact rejection based on signal amplitude should be used to exclude signals exceeding ± 50-100 μV in amplitude. The amplifiers must return to baseline rapidly following artifactual signals. Analogue high pass and low pass filters (–3 dB points) should be set at < 1 Hz (corresponding to a time constant 0.16 s or more) and at > 100 Hz. The number of sweeps per average depends on the signal to noise ratio between the VEPs and the background noise. In most clinical studies the minimum number of sweeps per average is recommended to be 64. The analysis period (sweep time) is recommended to be between 250-500 ms. At least two averaged should be performed to verify the reproducibility of VEPs [170].

For PVEPs dilated pupils are not required. They are necessary only in flashVEPs. Monocular stimulation is standard. Simultaneous recording of PERG and PVEPs is possible. In this case it is also preferred monocular stimulation. Adequate optical correction is recommended. The patient should be seated comfortably so no muscle and other artifacts. For maximum results objectivity it is important that patients are cooperative [38].

In PVEPs is measured the amplitude of the three components (peak to peak) and the peak-time in the Anglo-Saxon literature or peak latency (PL), also known as implicit time in ERG. The peak-time is the time measured from the beginning of the stimulus to its peak, and the latency is the time from the beginning of the stimulus to the beginning of the response. Standard exact term is peak-time. In our terms peak time and latency are used synonymously. The most stable component is P100. It is advisable to measure the amplitude of P100 from the preceding N75. P100 is usually a positive peak showing relatively little variation between subjects, minimal within-subject interocular difference in healthy subjects and minimal variation with repeated measurements over time [170, 224].

Multi-channel VEPs recording is used to assess the optic chiasm or retrochiasmal disorders. Chiasmal dysfunction gives a “crossed” asymmetry whereby the lateral asymmetry obtained on stimulation of one eye is reversed when the other eye is stimulated. Retrochiasmal dysfunction gives an “uncrossed” asymmetry, such that the resulting VEPs obtained on stimulating of each eye show similar asymmetrical distribution across the two hemispheres. Although there is no

standard for multi-channel VEPs, the ISCEV standard suggests the pattern stimuli to be presented with a field of 30° (double the minimum size required by the standard). A minimum of two channels is needed for detection of lateral asymmetries. The authors of ISCEV suggest at least three active electrodes: two lateral electrodes placed et O1 and O2 and a third electrode located at the midline Oz. All three active electrodes must be referenced to Fz. Additional electrodes placed at PO7 and PO8 (parietal scalp), also referred to Fz, may increase sensitivity to lateral asymmetries [170].

Particular caution is needed when interpreting multi-channel PRVEPs because of paradoxical lateralization. This is a phenomenon in which the signal recorded by a lateral electrode is generated by activity in the contralateral hemisphere. This can be obtained using a large field of stimulation, or a long period of reversion [41, 58, 64, 70, 112, 146, 170, 223, 225].

Factors affecting the amplitude of P100 are: visual acuity, pupil size (asymmetry of pupils can lead to asymmetry of P100 responses). P100 is influenced by many other parameters such as the size of the checks in the checkerboard pattern, the contrast, illumination, the signal filtration, age, refractive errors, poor fixation, electrodes position on the scalp, anatomical variations as thick skull bones and orientation of the occipital cortex towards the scalp and others. The size of checks is measured by degrees of the angle (minutes of the arc). The fovea is the most sensitive to the small checks. They are associated with a lower amplitude and longer L of VEPs. They are extremely sensitive in ophthalmological diseases, including reduced visual acuity. The reversion of the larger checks stimulates the paracentral and peripheral portions of the retina. The L shortens with the increase of the stimulus illumination intensity. The L increases with age over 40. The females have shorter L of P100 to men as well as higher A. The L and especially the amplitude of N75 and N145 are much more variable. It is assumed that the L of VEPs shows the conduction velocity through the ocular routes, while the amplitude may be associated with the conducting axons number [58, 104, 224].

PVEPs onset/offset consists of three main peaks – C1 (positive, approximately 75 ms), C2 (negative, 125 ms) and C3 (positive, 150 ms) [170].

FlashVEPs consists of a series of positive and negative waves. The earliest detectable component has a latency of approximately 30 ms poststimulus and components are recordable with latency of up to 300 ms. The peaks are defined as negatve and positive in a numerical sequence. This nomenclature is recommended to distinguish flashVEPs from PRVEPs. The most reliable components of flashVEPs are N2 and P2. Measurements of P2 amplitude should be made from the positive peak P2 at around 120 ms to the preceding N2 negative peak at around 90 ms [170].

Multifocal VEPs

The multifocal VEPs (mfVEPs) are relatively new method that objectively record cortical responses from the central visual field [21]. This method provides topographic information from the central visual field and evaluates the localized responses [22]. The visual stimuli are produced on a monitor, but can also be used infrared camera. The stimulating image has the appearance of a dartboard containing 60 segments. These segments are cortically scaled in order to produce 60 recordings of approximately similar amplitude from the visual cortex. Each segment contains a checkerboard pattern of 16 checks, 8 white (138.0 cd/m^2) and 8 black (3.5 cd/m^2), that contrast reversed in a pseudorandom binary m-sequence at a frequency of 75 Hz. The signals are

amplified 100000 times and are passed through a band pass filter with cut-offs of 3 Hz and 100 Hz. Each run contains 16 segments in 27 seconds with a total recording time 7.2 minutes. The viewing distance is 40 cm using monitor and 5 cm using IR camera [72, 214]. All recordings are bipolar with little difference in electrode positions according to various authors. According to some of them the electrodes are placed 2 cm above and 2 cm below the inion – to minimize the response difference from the upper and lower cortical hemifields [123]. According to another authors the lowest electrode is placed at the inion, and the other 4 cm above the inion [101]. These electrode positions evoke higher differences between the amplitudes from the upper and lower hemifields but there are much less muscle disturbance in the responses. Many electrode positions have been described from different authors, since there is still not established standard for mfVEPs. The ground electrode is always located behind the right ear. During the study, the patient should be seated comfortably to minimize muscle interference, fixating the center of the dartboard. Dilated pupils are not required, the stimulation is monocular with the fellow eye occluded. A dim room light is used as background illumination [72, 214].

Although standardization should ensure similar VEPs waveforms across laboratories, each laboratory must establish its own normative values using its own stimulus and recording parameters.

Visual evoked potentials in ophthalmic and ophthalmoneurology diseases

Changes in VEPs occur in a number of retinal diseases [164, 166, 167]. There are studies showing that the L of P100 was normal in patients with lamellar macular hole and prolonged in a full hole. Furthermore, it is found that the L is longer in patients with optic neuritis, then in those with complete macular hole [111]. Other authors did not find such law, taking into account the patients optical correction [200]. Since changes in macula result in a change in VEPs, monocular VEPs abnormality in absence of other information about the location of the lesion is interpreted as an indication of prechiasmal dysfunction. The same abnormality of VEPs, but in a presence of normal ERG directs us to retrobulbar damage [58]. VEPs, together with ERG, were investigated in patients with AMD and hereditary eye diseases, such as pigmented retinitis, macular dystrophies and others [34, 220]. Johnson et al. [110] described PVEPs in a whole family with pigmented retinitis as different members have different affected VA and perimeter, and one of them looks perfectly health. They found that absolutely all members of the family had abnormal PVEPs. In glaucoma also recorded prolonged latency, as well as in diabetic macular edema [100]. Many studies describe the changes of VEPs in optic neuritis and multiple sclerosis (MS). Extended latency is the most common change, but there are also described cases of reduced P100 amplitude, especially in consecutive attack. At the first attack, in many cases after VA normalization, the L recovers, probably due to the onset of partial remyelination [124, 194]. Extended P100 latency is a very sensitive sign for detection of optic nerve demyelination [15, 79, 91]. Such demyelination which leads to a delay of the conductivity was observed in optic neuritis (ON), and MS, but also might be registered in ischemic optic neuropathy (IOP), optic nerve compression and spinocerebellar degeneration [15, 77]. Takasoh et al. [208] studied transient PVEPs in patients with OH and anterior ischemic opticopathy (AIO). Making a comparison between the two groups they concluded that in both groups there were greatly reduced A and L, but the L in AIO was significantly shorter than in ON and the A was lower in AIO. This could be used in differential diagnosis. Other authors came to the same conclusion [69, 230]. Ikejiri et al. [105] studied PVEPs in patients with traumatic optic neuropathy and compared it with OH. They found reduced A more pronounced than in ON.

In optic nerve compression seen most commonly in pituitary tumors, Barett et al. [20] for the first time used transient PVEPs. They found distinct asymmetry in distribution on the scalp in 10 patients with chiasmal dysfunction using 15° viewing field. In particular, they first described the "cross" VEPs asymmetry typical for chiasmal dysfunction, where the results of the one eye were abnormal in the one hemisphere, but the asymmetric distribution was found when the fellow eye was stimulated. They reported a "paradoxical lateralization" so that the maximum abnormality is localized ipsilaterally to the visual field defect. Similar findings of many authors subsequently confirmed that the "cross" PVEPs asymmetry is pathognomonic in chiasmal dysfunction [20, 29, 59, 76, 78, 138, 172].

In albinism patients have abnormal targeting of optical nerve fibers, so that the majority of the optic fibers of each eye are projected onto the contralateral hemisphere. In normal pigmented individuals approximately 50% of the optic nerve fibers are projected onto the ipsilateral hemisphere and about 50% – on the contralateral. PVEPs most ostentatiously show these changes [51].

Martinelli et al. [143] studied PVEPs in MS patients with normal VA and found changes in PVEP in patients without a history of visual disturbances ever.

Negishi et al. [165] investigated transient and steady-state PVEPs in patients with macular disease (AMD, RCS, branch retinal vein occlusions) and compared the results with the VA and with the results in ON. They found elongated L and reduced A of P100 at steady-state PVEPs compared with healthy individuals. The latency was less extended than in OH, while the changes in the A were similar in the two diseases. The VA correlated with the changes in the L and A. Similar results were obtained by Nemoto et al. [166, 167] in a study of mfVEPs in patients with AMD.

Hanawa et al. [81] used PVEPs for prediction of the VA in patients with glaucoma and cataracts and concluded that the age and the P100 A correlated with the postoperative VA. The electrophysiological studies PERG and PVEPs were used preoperatively to predict the effect after keratoprosthesis [48].

Mizota et al. [154] studied patients with unilateral OH by monocular and binocular stimulation and found that there was no binocular summation of the responds if there was a big difference in the L between both eyes, although there was a good stereopsis.

VEPs can be used as an objective method for study of VA and simulation. Such studies were performed by Bach et al. [17]. De Araujo et al. [48] used VEPs and ERG as objective methods for preoperative evaluation of the visual analyzer function before putting keratoprosthesis.

Electrophysiological studies and diabetes mellitus

By EF studies can evaluate the function of the retina in diabetic patients in an objective manner using ERG, that reflects the EF activity of the neurons in the retina and VEPs, which indicate the electrical conductivity across the optic tract [137, 215]. Changes were found in both ffERG and in mfERG, even before establishing of DR [35, 111, 127, 176]. According to Walsh [224], PERG is a sensitive indicator of DR occurrence. Many EF studies that could prove the neuroretinal degeneration in an objective manner, are used recently in patients with prediabetes. Previous

studies have found changes in ffERG, which indicated the electrical response of the entire retina. The most frequently described was the oscillatory potentials delay [32, 63, 111, 132, 162, 199, 202]. The OPs are believed to originate from the amakrine cells in the inner layers of the retina. Increasing of the Muller cells activity was demonstrated in mice with streptozotocin-induced diabetes (streptozotocin is a substance toxic to pancreatic beta cells; single injection of 60-70 mg/kg is sufficient to induce insulin-dependent diabetes in 48 hours). This phenomenon led to a change of OPs, reducing of A and increasing in latency [201, 235]. Using the same type of laboratory animals Wright et al. [232] postulated the possible role of glutathione (GSH) in the genesis of ERG modifications: it was found a correlation between GSH and all ERG parameters, except the b-wave L, which did not change significantly in the presence of hyperglycemia [222]. It has been found extension of L in 30-Hz flicker responses in type 1 diabetes with advanced DR and duration of diabetes of 16 year [32, 107]. Holopigian et al. [103] found evidence of photoreceptor changes – delay of a- and b-waves in a group of 12 diabetics (4 type 1 and 8 type 2) with duration of diabetes over 5 years. Studies that used mfERG, which reflecting primarily the cone function showed extended L in patients with diabetes type 1 and type 2 lasting about 10-15 years [24, 61, 80, 101, 195]. In other studies in scotopic-adapted ffERG was found extended L of a-wave, indicating mainly affected rods in patients with newly diagnosed diabetes [106]. According to other studies the rods were affected stronger than cones in diabetic patients. This may be due to the more intensive rods metabolism and the fact that hypoxia within the retina is more expressed in dark [221]. In diabetic patients without DR was observed a reduced amplitude of b-wave, which is believed to represent affecting of the primarily cells of the inner retina layers [176]. According to another studies, there were no changes in the amplitudes of mfERG, or they even become larger compared to the control group [23, 117]. The higher amplitudes may be due to increased retinal perfusion as a result of impaired autoregulation [74, 125]. Elevated serum glucose levels lead to increased amplitudes due to higher retinal metabolism [122]. But other studies had not find such correlation – in these studies lower amplitudes compared to controls were detected only in patients with severe DR [33, 117]. Caputo et al. [37] found that PERG was especially sensitive at detecting changes in the preclinical stage of diabetes. They researched diabetic patients without DR and established significantly reduced A N95 compared to the control group, and found a big differences between the results of these patients and the patients with DR. The A was in an inverse proportion to the duration of diabetes. Progressive delay in VEPs, and reduced amplitudes, which appear mainly changes in the optic nerve, was observed in diabetic patients with or without DR, with or without neuropathy [1, 10, 44, 153, 197, 218]. In many studies were described VEPs in patients with diabetic neuropathy, without RD [184]. The authors studied VEPs in patients with diabetes without evidence of DR, with normal VA and with diabetic neuropathy and established extended L in all cases, in most of them with reduced A. They found good correlation between the conduction through the optic nerves and the peripheral sensory nerves. There was found absence of correlation with the duration of diabetes or the metabolic control, except perhaps in juvenile diabetes. Algan et al. [4] also established elongated L, but did not find to correlate with the type and duration of diabetes, as well as the metabolic control. Pan et al. [177] concluded that in diabetes the L and the interpeak latencies were extended, except of N75. Ziegler et al. [238] made study whether the momentary strict blood sugar control could improve the abnormal VEPs in patients with poor metabolic control without DR and DN and concluded that VEPs were partially reversible under strict metabolic control. The VEPs L still remained more elongated compared with the control group, but were shorter in comparison with the state of the same patient with poor metabolic control [144]. Yaltkaya et al. [233] concluded that the duration of diabetes

correlated with the changes in VEPs, but no correlation found with the changes in the conductivity of the peripheral nerves.

Normal visual acuity was observed in many cases with very slow conduction, indicating subclinical primary optic nerve damage in diabetes. It was found a high incidence of abnormality on VEPs in diabetes [88]. They researched PVEPs in patients with DM type 2 with normal VO without and with DR and established significant reduction of N75 and P100 amplitudes and longer latency in all diabetic patients without and with DR. No correlation was found between the EF changes and the level of glycemia or duration of DM. The authors concluded that the prolongation of P100 latency was an expression of structural damage at the level of myelinated optic nerve fibers. Their results also implied that there was a neurological deficit in type 2 DM patients which could involve the central nervous system at an early stage without DR manifestation. The pathophysiology of central nervous system dysfunction is unclear but is multifactorial, involving metabolic and vascular factors, similar to the pathogenesis of peripheral DN in which ischemia and reduced protein synthesis resulted in nerve fiber loss in peripheral nerves. This caused the conduction delay in the visual pathway. About central neuropathy in diabetes spoke De Jong, which described clinical and pathomorphological evidences of diabetic myelopathy and encephalopathy [49]. According to Puvanendran et al. [184] changes in the optic nerves occurred as often as in peripheral nerves in diabetics as no patients had clinical evidence of optic neuritis and their VA was normal. The conductivity of the optic nerve was parallel with the peripheral nervous conduction, but not with the spinal somatosensory conduction.

DM as a cause of optic neuropathy is very rarely mentioned among ophthalmologists. Some even doubt the existence of such a possibility [87]. But Reske-Nielsen et al. [188] observed severe demyelination and degeneration of axons in the axes of the visual chiasm and severe demyelination of other cranial nerves with long-standing type 1 diabetes. Such cranial neuropathy could be observed asymptomatic as well as symptomatic. Subclinical sensory neuropathy occurred at the beginning of diabetes due to segmental demyelination and might also affect the optic tract. Demyelination was a result of either conduction block, if the lesion was large, or delayed conduction if the lesion was small. Demyelinated fibers might conduct series of pulses with a physiological rate, resulting in a block [150, 165]. Other authors also examined type 1 diabetic patients with DN and without DR and looked for correlation between changes in transient PVEPs and the metabolic control and the duration of DM and concluded that there was subclinical damage of the optic path in almost all patients with prolongation of L and reduction of A of P100 [45]. The interpeak latency N75-N145 was also extended. There was no apparent correlation between L and age, the values of HbA1c or the insulin dose, but there was correlation with the duration of diabetes. The authors explained these changes with desynchronization in conducting impulses in the optic pathway. Ewing et al. [56] made a comparative study of changes in PERG, flashERG and PVEPs in both types of diabetes and concluded that changes in PVEPs occurred earlier than those in PERG in both types of diabetes, but according to other authors earlier changes occurred in DM type 1 only [32]. They found that PERG was more sensitive than flashERG in manifestations of hyperglycemia. The authors concluded that ERG changes occurred without presence of DR. Jenkins et al. [108] concluded that the changes in flashERG occurred in patients without DR or in patients with minimal DR in more than a half of their patients. Arden et al. [14] studied the changes in PERG in patients at different stages – from those without DR to those with PDR and concluded that PERG was normal in minimal DR (microaneurysms and single haemorrhages) and started to become abnormal with the appearance

of soft exudates. Such changes ascertained in OPs also, but the results were more variable. The authors considered that PERG could be used as a screening for the progression of DR. Lawwill and O'Connor [130] investigated the influence of laser photocoagulation on ERG A and reached the conclusion that if approximately 20% of the area of the retina is coagulated a 10% reduction in A of a- and b-wave was observed. Slightly larger reduction of A established Wepman et al. [227] at approximately the same area photocoagulated retina.

The majority of these EF studies have focused on diabetic patients with long-standing diabetes, with or without RD.

Conclusion

According to many authors PERG is generated by the activity of RGC, which are damaged early in diabetes. Most authors considered that PERG derived largely from the ganglion cell induced by the photoreceptors and the corresponding retinal cells and affects the integrity of the three neurons in the retina - photoreceptors, bipolar cells and ganglion cells. Analyzing the literature, we come to the conclusion that PRVEPs are the preferred stimuli in the most clinical studies. They are the least variable in shape and time in comparison with the other types of VEPs.

In Bulgaria researches of the visual analyzer with PERG have not been done. There are no studies of PVEPs in patients with DM also. At the same time the literature survey found that the EF studies are an actual topic. EF methods are reliable diagnostic method in many ophthalmic and ophthalmoneurological diseases. In DM there are changes in the outer retina (photoreceptors and bipolar cells) and the inner retina (ganglion cells) and along the optic path to the cortex in patients with both newly diagnosed diabetes and diabetes type 1 and type 2 with different duration with or without the presence of DR. Some of the changes have been presented since the diagnosis of the disease, before presence of the vascular changes in the retina. This indicates that the neuronal damage may develop parallel or even prior to vascular changes. There are contradictory results of studies of various authors on the dependence on the EF researches from the duration of DM, the type of DM, the metabolic control, the presence of changes in the conductivity of the peripheral nerves. Similar are the results related to the risk factors impact to the DR progression, but it was not found clarified issue about the impact of the risk factors to the progression of changes in EF researches.

There are single simultaneous studies of ERG and VEPs in patients with DM in the literature. According to several authors PERG and PVEPs are sensitive indicator of DR onset and especially in detecting changes in the preclinical stage of diabetes. Therefore, they can be used for early diagnosis of DR and prognosis and following during treatment. Some authors considered that these tests might be used as screening for progression of DR. EF studies show abnormality in functioning of the entire visual systems in diabetic patients at different stages.

Given the insufficiently explored questions, unexplained assumptions and conflicting opinions, it can be concluded that they are justified on the impact of DM on the visual analyzer function.

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