Review Article. Role of Electrophysiological Methods in Diagnosis of Hereditary Retinal Dystrophies

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Abstract: *The aim of the study is to present the different electrophysiological methods (EF) for study the retinal function and to highlight their importance in the diagnosis of hereditary retinal dystrophies (HRDs). EF methods are objective methods including the different types of electroretinography (ERG) and electrooculography (EOG). They are "the golden standard" in the diagnosis of retinal dystrophies. EF are especially valuable in the initial stages of the diseases and in asymptomatic forms. They are also particularly important for monitoring the changes in dynamics, which is very important for the diseases prognosis. HRDs are a heterogeneous group of diseases with a relatively low frequency in the human population, characterized by involvement of different retinal layers, most often the complex retinal pigment epithelium-photoreceptors and causing severe visual impairment – loss of night vision, visual field, color vision and visual acuity in the initial stages and leading to progressive and severe loss of visual function by altering the retinal anatomy and function. By EF studies can evaluate the function of the retina in patients with these "rare eye diseases". EF methods are most important in the diagnosis of HRDs. They are also important in the differential diagnosis between the different retinal dystrophies. A major challenge for the ophthalmologists is to identify the diseases in the early stages. There is an urgent need for more knowledge and practical use of these methods for accurate diagnosis which is a prerequisite for a proper therapy.*

Keywords: *Electroretinography, Electrooculography, Hereditary retinal dystrophies, Electrophysiology.*

Introduction

"Rare eye diseases" are diseases with a relatively low frequency in the human population. "Rare diseases" are those with a frequency of less than 1:2000 population. About 900 "rare eye diseases" are known. Hereditary retinal dystrophies (HRDs) have the largest part. According to different sources, about 750 are the retinal, choroidal, or both dystrophies with a specific gene defect identified in about 270 of them. The correct diagnosis of these diseases is extremely important as they are severely disabling the individual [18].

The aim of the study is to present the different electrophysiological methods (EF) methods for study the retinal function and to highlight their importance in the diagnosis of HRDs.

Hereditary retinal dystrophies

Hereditary retinal dystrophies are a heterogeneous group of inherited diseases characterized by damage of different retinal layers, most often the complex retinal pigment epithelium (RPE) – photoreceptors and cause severe visual impairment – loss of night vision, visual field, color

vision and visual acuity in the initial stages and lead to progressive and severe loss of visual function by altering the anatomy and function of the retina [1].

Classification of hereditary retinal dystrophies

Different classifications are available, but the most commonly used is the anatomical one, which is based on the primary affected layer – retina, macula, retinal pigment epithelium (RPE), choroid, vitreous/retina. But this approach is not always the most correct, because in some dystrophies several layers or areas are affected at the same time [1].

Another type of classification is based on heredity. Many genealogies have been studied, which clarifies the type of inheritance past to generations [8].

There is a third type of classification, which is based on the phenotypic assessment performed after clinical examination, electrophysiological and psychophysical studies. Careful analysis of all these studies results makes it possible to assign them to a particular nosological group clinically, and later to be confirmed by molecular genetics [1].

For clinical identification purposes, dystrophies with primary diffuse photoreceptor involvement are classified separately from those with predominant central (macular) involvement, as they differ significantly by symptoms and prognosis.

Diffuse photoreceptor dystrophy is divided according to the primary affected type of photoreceptors into cone-rod and rod-cone dystrophies.

There are also groups with primary choroidal involvement, as well as vitreoretinal dystrophies. Depending on the course of the disease, they are divided into stationary and progressive.

Some of the dystrophies appear in early childhood, while others have a later onset and a better prognosis. The family history is extremely important because most of them have a pronounced heredity.

Hereditary eye diseases have bilateral symmetrical involvement and if the process is unilateral, other causes should be sought – intrauterine infections, trauma or inflammatory diseases.

There are isolated forms with ocular involvement only, as well as syndromic dystrophies, which are part of a systemic disease involving other tissues and organs [1, 8].

Electrophysiological methods for study the retinal function

EF methods are objective methods for studying the retinal function. These include the different types of electroretinography (ERG) and electrooculography (EOG).

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 intraretinal ions flow, 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 corneal surface. 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 diagnostics and monitoring the progression of various retinal diseases [14].

ERG represents an analog curve containing the following components:
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 cGMP level 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 [14].

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 [14]. The b-wave reflects the condition of cells of the inner layers of the retina, including bipolar cells and Muller cells [40]. 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 [14].

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 RPE cells and hyperpolarization of the distal portion of Muller cells. C-wave normally reaches its peak within 2 to 10 seconds of light stimulus, depending on the light intensity and duration. 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 c-wave measurements (Fig. 1) [14].

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 wave (Fig. 1) [14].

Amplitudes of the responses are measured in microvolts (μV), and L in milliseconds (ms) (Fig. 1) [38].

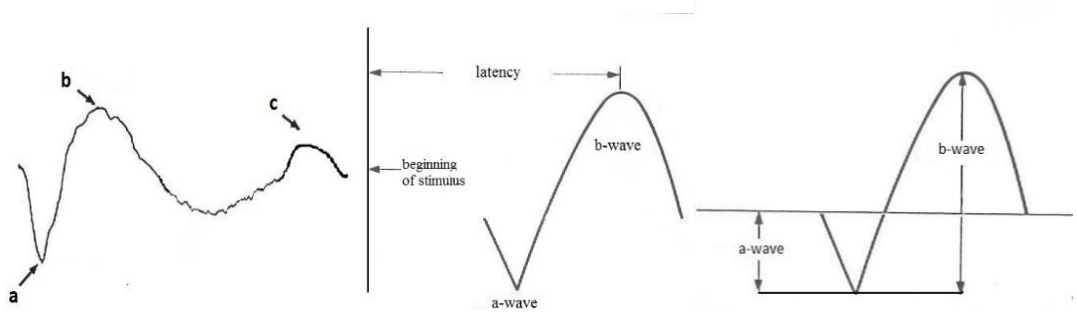

Fig. 1 Normal ERG configuration, measurement of latency and amplitude

ERG wave can be of several types:

Hypernormal – with increased amplitude of both a-wave and b-wave. This can be caused by irritation of the retinal structures by inflammation, intoxication, hypoxia, metabolic disturbances or disruption of retino-thalamic feedback. It can occur in the early stages of degenerative and dystrophic diseases of the retina, intoxication of the body and metallosis of the eye.

Subnormal – when the amplitudes of both a- and b-waves are decreased. This is the most common type of pathological ERG. The degree of reduction in potential depends on the nature and stage of the pathological process. It can occur in dystrophic changes of the retina and choroid, chronic vascular diseases of the retina, retinal detachment, high myopia and others.

Negative – a normal A of a-wave is observed, but the A of b-wave is reduced. This type of ERG is typical for acute vascular diseases of the eye such as occlusion of the central retinal vein and artery, as well as in congenital stationary night blindness.

Non-registered – in case of irreversible processes in the retina no electrical activity is registered, e.g. in advanced retinitis pigmentosa (RP) [14].

According to the type of A we can orient about the extent of the retinal involvement. A slight drop in detects initial functional changes; a great reduction of A indicates an appreciable affection of the retinal function and unregistered wave indicates irreversible retinal changes [14].

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 [14].

Different shapes and sizes of corneal contact electrodes, bearing the names of their creators, are in use, also surface electrodes. It is very important to consider what electrodes are used in the study, as ERG waves look different at different types of electrodes used [14, 37].

The functional response of rods and cones can be divided using different ERG-techniques, reflecting the activity of the different cells in the retina. Their knowledge and proper use in different nosologies is a prerequisite for good diagnosis and prognosis [3].

As they are especially important in the diagnosis of retinal dystrophies, we will focus on each of them in more details [38].

Full-field ERG

Full-field ERG (ffERG) 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 electroretinography recordings were made in frog by Holmgren in 1865 [22]. The technique is based on registration of the overall potentials generated by the retinal cells after light stimulation. To obtain the best sensitivity of photoreceptors, the retina was dark-adapted for 30-45 minutes before light stimulation. This is the time required to perform a chemical process to restore the photopigments. The entire retina is illuminated by light produced by Ganzfeld-field and bipolar electrode - contact lens that detects at the corneal surface the electrical activity generated by the retina [33, 38].

To affect the A of a- and b-waves, damage is required in a large area of the retina, so that a focal lesion of the fovea (about 1.5 mm in diameter) does not cause a change in the A of waves. According to some authors, the photoreceptors of at least half of the retina must be affected in order to obtain a reduction in ERG in the full-field technique [28]. Normal ERG can be obtained in diseases with significantly reduced visual acuity (VA) in this technique, and vice versa – in normal VA and diffuse involvement of photoreceptors unregistered ERG can be obtained, e.g. in RP [29, 36].

ffERG measures the activity from the entire retina and is useful in detection of diseases with generalized retinal dysfunction such as RP, hereditary photoreceptor dystrophies – cone and rod, Leber congenital amaurosis, toxic retinopathies and others [6, 13, 41, 43, 45, 48]. 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 6 different tests [38].

Dark-adapted 0.01 ERG – dark-adapted response after low-intensity light stimulation – (scotopic rod response) is isolated after dark adaptation for a minimum of 20 minutes according to ISCEV standard, followed by a shortwave stimulus as a single flash or 10 Hz low intensity flicker. The flash power is 0.001 photopic cd s m^2. The minimum interval between stimuli is 2 seconds, and the duration of the stimulus is not more than 5 ms. This is the first response that occurs after dark adaptation. Although there is a rod and cone component in the obtained response, the rod component is dominant and is the main factor for potential formation. It is believed that after 7 minutes of dark adaptation, the bioelectrical activity of the rods begins to prevail. They respond better to lower stimulus intensities – white or blue light [38].

Dark-adapted 3.0 ERG – a combined response of rods and cones, slightly dominated by rods. It is isolated again after dark adaptation for a minimum of 20 minutes. It is recorded immediately after the first scotopic response. As the light stimulation is of low intensity, it is also considered to be a scotopic response. In this case, the light intensity of the flash is 3.0 photopic cd·s·m^2, with an interval between stimuli of 10 seconds [38].

Dark-adapted 10.0 ERG – a combined response of rods and cones, with a pronounced a-wave reflecting the photoreceptor function. It is recorded after the second scotopic response, after dark adaptation for a minimum of 20 minutes. The stimulus has a slightly higher intensity of 10.0 photopic cd·s·m^2 and an interval between stimuli of at least 20 seconds. This type of stimulation is very informative in opalescent eye media and immature retina [38].

Dark-adapted 3.0 oscillatory potentials – a response primarily from the amacrine cells. The oscillatory potentials (OPs) were first described in 1954 by Cobb WA and Morton HB, later named so in [16]. They are generated by a flash with a light intensity of 3.0 photopic cd·s·m^2 and an interval between stimuli of at least 10 seconds. They have a high frequency of about 100 to 160 Hz, low-amplitude waves. Although not known with certainty, it has been suggested that OPs are generated by amacrine cells located in the inner retina. These waves appear to reflect the negative feedback activity exerted by the amacrine cells to the bipolar and ganglion cells. By increasing the low bandwidth range from the usual < 1 Hz to about 100 Hz, the slower a- and b-wave components are filtered, leaving a series of conical oscillatory potentials. Although OPs are generated by cells in the inner retina, their A decreases in diseases, affecting the outer retina such as RP or cone dystrophy, because their involvement prevents the impulse transmission through the chain more proximally, so the A of a- and b-wave was also changed, as well as OPs [34, 38, 51].

Photopic 3.0 ERG (cone response) – the cone function is measured after light adaptation for at least 10 minutes and with a single flash with an intensity of 3.0 photopic cd·s·m^2 and an interval between stimuli of at least 0.5 seconds. The cones respond better to a bright stimulus – white or red. Photopic responses lead to small b-wave amplitudes with short latency (30-32 ms), unlike the scotopic (rod) conditions that cause much larger b-wave A with extended latency (60 ms) [15, 38].

Photopic 30 Hz flicker ERG (sensitive cone response) – since the rods cannot vibrate with a stimulus with a frequency greater than 20 Hz, this is a sensitive cone response with a stimulus frequency of 30 per second. A stimulus with a wavelength greater than 680 nm is used [38].

Typically, in ffERG, the three consecutive scotopic ERG examinations are performed immediately after the dark adaptation, followed by 10 minutes of light adaptation, followed by the two photopic ERG examinations.

Focal ERG

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 in 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 macular dystrophies, but requires good patient fixation [14, 42, 52].

Multifocal ERG

The multifocal ERG (mfERG) was introduced by Sutter and Tran in 1992 [47]. 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 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 is in topographic 3D format that shows the overall signal strength per unit area of the retina [21, 23, 24, 33, 34].

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 ffERG cone response on the other [25]. 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. The latency sometimes better describes the progression of the retinal diseases [50].

MfERG is very useful in diagnosis of macular diseases, as well as for detection of localized abnormalities in the retina. In macular disease, central retinal dysfunction presents as signal loss or decreased A in the central part of mfERG. In RP with peripheral dysfunction and preserved macular function, mfERG appears with a steep central peak and a weak or missing signal from the periphery or the peripheral rings. For example, in Stargardt disease, which is a hereditary maculopathy with predominantly cone involvement, the biopotentials in the central part have elongated L and reduced A, and the peripheral ones are much more preserved [43].

Pattern ERG

Pattern ERG (PERG) is a retinal biopotential evoked by a contrast-reversing pattern from black to white and vice versa, projected on a screen at a constant illumination and central fixation. PERG does 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 [19]. The standard recommended rate of reversion is 16 rps (8 Hz) ± 20% for "steady-state PERG". At least two trials for each stimulus condition should be obtained to confirm reproducibility [5, 14].

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 [5].

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. 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) [5]. PERG is generated by the retinal ganglion cells activity. The most commonly measured is P50, which is very similar to the b-wave. It is debatable which one component detects the ganglion cells activity but nowadays it 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 [14].

According to the ISCEV standard there are no standard international reference values for PERG measurements. Each laboratory must establish normal values for its equipment and population [5].

As PERG 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 [20, 44].

Electrooculography

Electrooculography has been popularized in clinical practice by Arden et al [4]. Unlike ERG, EOG is not a stimulated response, but records the constant potential that exists in the eyeball. The eye is a dipole with a negatively polarized retina and a positively polarized cornea. The advantage of EOG over ERG is that the electrodes are not in contact with the eyeball. Skin electrodes are used, which register the change in the constant potential between the cornea and retina in the eyeball as a result of the eye movements. At this method, potentials generated during the eye movements are recorded by placing electrodes on both sides of the eye – active and reference electrodes. First, the patient is light-adapted and a baseline recording is made. Then begins a 15-minute dark phase during which every 1 minute a recording is made when moving the eyes for 10 seconds. This is followed by a 15 minute phase in bright light and again records are made every 1 minute for 10 seconds. The movement of the eyes causes a voltage of about 5 millivolts between the electrodes on both sides of the eye. In healthy eyes, the A potentials are lowest during the dark phase, which is called maximal scotopic decrease (MSD). With the onset of the photopic phase A increases gradually and reach a peak about 7-12 minutes from the beginning of the photopic phase, called the maximum photopic peak (MFP) [11, 39].

The potentials recorded during EOG are used to calculate the Arden ratio. It is obtained by dividing the peak A under photopic conditions to the maximal decrease in amplitude during the dark adaptation MFP/MSD. The Arden ratio may vary depending on the methodology, including the duration of adaptation, pupil size, and light intensity. According to ISCEV standard most often the lowest value of Arden ratio is about 1.7 in normal subjects [11, 39].

EOG mainly reflects the RPE function, but depends on the integrity of the RPE, photoreceptors and interphotoreceptor matrix. For this reason, EOG is pathological in photoreceptor diseases, retinal detachment and other generalized diseases of the external retina and RPE such as Best disease. ffERG is in many cases normal in the early stages of this disease. That is why the EOG test is very important for the diagnosis because it demonstrates a characteristic abnormal waveform at each stage of the disease as the Arden coefficient is usually less than 1.5, most often between 1.0 and 1.3. It is also used to study drug toxicity [11].

Electrophysiological methods in the diagnosis of hereditary retinal dystrophies

Electrophysiological methods are most important in the diagnosis of HRD's. They are "the golden standard", especially valuable in the initial stages or in asymptomatic forms, when subjective symptoms are absent and in many cases with a normal fundus. They are also particularly important for monitoring the changes in dynamics, which is very useful for the prognosis of the damage. EF methods are very informative, because duo to a correct selection of the appropriate EF study can make a differential diagnosis between different types of hereditary retinal dystrophies, which is sometimes very difficult, but is especially important in choosing the appropriate therapy. After the family history and clinical examination, EF methods are the next test to differentiate the retinal dystrophies [1, 2, 14].

In generalized retinal dystrophies the most informative is ffERG, while in hereditary macular dystrophies the most important is the role of mfERG and EOG.

In RP the most informative study is ffERG, which is affected even in asymptomatic carrier of the pathological gene. In the early stages of the disease is registered reduced scotopic response which becomes unregistered in the more advanced cases. As RP is a rod-cone dystrophy,

depending on the degree of cone involvement, the photopic response is affected to varying degrees [14].

Changes in ERG may precede the characteristic retinal pigment changes in all genetic variants (retinitis pigmentosa sine pigmento). In most cases, in patients with autosomal recessive (AR) or X-recessive (XR) inheritance, an unregistered ERG or ERG with very low A is found in the initial stage of the disease [11, 35]. In the recessive type of inheritance, different variants of ERG can be observed. For example, Cideciyan et al. [10] observed negative ERG waves in 7 patients with RP.

Other authors studied an extended family with RP 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 were changed the scotopic responses only, but in the latter stages the photopic responses were also affected. They found in XR inheritance in 71% of cases unregistered ERG and in the remaining 29%, in which there were preserved waves in half of them the cone response was more affected than that of the rods, and in the other half the rods were more affected [7]. Gundogan et al. [16] also described a patient with advanced RP with unregistered scotopic response and reduced photopic response, which detects rod and cone involvement.

In many syndromes, similar changes can be found, as they occur with different involvement of ERG – from slightly reduced A to unregistered ERG. Such are Usher, Laurence-Moon-Bardet-Biedl, Alstrom, Bassen-Kornzweig, Joubert, Senior-Loken, Cohen syndromes. In some of the mucopolysaccharidosis, similar ERG changes were observed [27].

There are numerous studies on hereditary rods and cones dystrophies, Stargard disease, Leber congenital amaurosis, which demonstrated the importance of EF studies for the proper diagnosis of the disease. ERG, along with EOG are the methods by which the predominant involvement of rods or cones is defined [9, 43, 46, 54].

Creel [12] described another case with an advanced form of RP and an unregistered response to scotopic stimulation and a greatly reduced response to photopic stimulation, which indicates very low residual cone activity.

Whatham et al. [53] presented ffERG of two cases of RP with different severity – the first case was at initial stage with preserved residual activity of cones – the photopic response had a lower A and delayed latency, but was registered. The combined response of rods and cones was also reduced, but registered (again due to the preserved residual activity of cones). The oscillatory potentials also had a reduced A. The most affected was the scotopic response – a non-registering wave. In the more severe second case the scotopic and photopic responses were severely affected – unregistered waves. There were only preserved, but much modified OPs.

In Leber congenital amaurosis which is a rod-cone dystrophy both the scotopic and photopic responses are affected in ffERG, but there is some residual cone activity. In many children, no ERG activity is recorded at birth. This distinguishes this disease from other generalized retinal dystrophies, in which the electrophysiological activity decreases slowly and gradually with age such as RP, albinism and others [29, 31, 32].

In cone dystrophies in ffERG the photopic activity is usually unrecorded, while scotopic activity is normal or slightly subnormal. They are much less common than combined retinal

dystrophies, which affect both types of photoreceptor cells. In the advanced stages, the function of rods is almost always affected. That is the reason why, according to some authors, cone dystrophies are also cone-rod dystrophies with much more severe and earlier involvement of the cones [26, 45].

In cone-rode dystrophy case, described by Fishman et al. [14] in ffERG, the cone response was almost unregistered. The most affected was the sensitive photopic response – 30 Hz flicker. The scotopic ERG in the initial stages was preserved, but later it was also changed, but significantly more preserved than the photopic one, indicating that the process was advanced with involvement of the rods as well.

Gundogan et al. [16] described a case of cone dystrophy with a normal fundus appearance. A preserved scotopic and combined responses and an unregistered photopic responses were demonstrated at ffERG. The combined response had a slightly reduced A due to the affected cones influence.

In another case of cone dystrophy, described by Creel [12] the photopic responses were non-registerable, as well as OPs. Preserved, although altered, with prolonged latency and slightly reduced A, were the combined and scotopic responses.

In a patient with congenital stationary night blindness, described by Gundogan et al. [16] in ffERG the scotopic response was non-registered, a negative b-wave was observed in the combined response (when A of b-wave is lower than A of a-wave, the peak of b-wave is below the isoelectric line and the amplitude ratio b/a is below 1). The photopic responses were slightly changed with a slightly reduced A. The negative b-wave in ffERG is also observed in juvenile retinoschisis.

In Oguchi disease, the photopic ERG is normal or slightly subnormal, but the scotopic ERG has a much reduced A, mainly the b-wave, with a negative b-wave of ffERG. Characteristically, the function of the rods is very weak in short-term dark adaptation, but as the duration of adaptation progresses, their function is restored to almost normal levels. Negative b-wave of ffERG is also characteristic for the Kandori's retina. It also sometimes has a prolonged adaptation of photoreceptors [1].

Fishman et al. [14] described patient with fundus albipunctatus. It is also a part of the Congenital stationary night blindness diseases group, due to the fact that it does not progress. It is characterized by disturbed adaptation (prolonged) of both rods and cones. Recovery of ERG and EOG responses is severely delayed, which corresponds to the time required for regeneration of visual pigments.

In Stargardt disease mfERG is very indicative, as it detects early changes in the function of the central macula, expressed in a decrease of the central peak A. In ffERG the photopic response is normal or subnormal, the scotopic response is usually normal. EOG is usually subnormal [12].

In PERG, which reflects the activity of the inner layers of the retina and is particularly sensitive in maculopathies, reduced A is obtained [20, 44].

In Bietti's crystalline corneo-retinal dystrophy, ffERG has a reduced A, more in the photopic response, but with pronounced peripheral changes, a reduced scotopic response to an unregistered ERG is also observed [1].

Best disease is characterized by a big dissociation between the severely altered fundus and the preserved visual function. ERG is usually normal. The most informative is EOG, which serves as a marker for the detection of this disease. The response in EOG is always abnormal, the light peak is greatly reduced or absent, which leads to a decrease in Arden coefficient, even in a normal fundus. Therefore, EOG is also used to detect the gene carrier between the parents in an established disease in the child. It can also be used to diagnose atypical undifferentiated macular lesions, if EOG is altered, it is most likely Best disease [17, 49].

Lucie [30] presented the EOG result of a patient with Best disease with a reduced light peak and an Arden ratio = 1.33. Gundogan et al. [16] described another more advanced case of best disease with a typical appearance of the fundus and EOG with an Arden coefficient = 1.18 for the right eye and coefficient of Arden = 1.17 for the left eye.

Conclusion

In this review we tried to highlight the importance of the electrophysiological methods in the diagnosis of hereditary retinal dystrophies. They are especially valuable in the initial stages of the diseases and in asymptomatic forms. They are also particularly important for monitoring the changes in dynamics, which is very important for the diseases prognosis. Their role is of particular importance in the differential diagnosis between the different retinal dystrophies, because sometimes it is not easy. A major challenge for the ophthalmologists is to identify the diseases in the early stages. There is an urgent need for more knowledge and practical use of these methods for accurate diagnosis which is a prerequisite for a proper therapy.

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