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# Clinical electrophysiological testing of the visual system: Review of the methods and indications for referral

## Klinično elektrofiziološko testiranje vida: Pregled metod in indikacije za napotitev

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## Abstract

Clinical electrophysiological testing of the visual system includes a series of non-invasive tests that provide an objective assessment of the functioning of the visual system. The recording of the electrooculography (EOG), electroretinography (ERG) and visual evoked potentials (VEP) can evaluate the function of vision from the level of the retinal pigment epithelium, retinal layers, optic nerves and visual pathways to the primary visual cortex. Testing is performed according to the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV), which recently issued guidelines for referrals to electrophysiological testing in ophthalmic practice. This paper presents the current methodology of electrophysiological testing and summarizes most frequent diagnoses for which a referral to electrophysiological visual testing is indicated.

## Izvleček

Klinično elektrofiziološko testiranje vidnega sistema vključuje vrsto neinvazivnih testov, ki zagotavljajo objektivno oceno delovanja vidnega sistema. S snemanjem elektrookulografije (EOG), elektroretinografije (ERG) in vidnih evociranih potencialov (VEP) je mogoče ovrednotiti delovanje vidnega sistema od ravni retinalnega pigmentnega epitela, posameznih plasti mrežnice, vidnih živcev in vidne poti do primarne vidne skorje. Testiranje se izvaja po standardih Mednarodnega združenja za klinično elektrofiziologijo vida (ISCEV), ki je nedavno izdalo tudi smernice za napotitev na elektrofiziološko testiranje v oftalmološki praksi. Prispevek predstavlja metodologijo elektrofiziološkega testiranja ter povzetek najpogostejših diagnoz, pri katerih je bolnika smiselno napotititi na to testiranje.

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## 1 Introduction

Clinical electrophysiological testing of the visual system includes a series of non-invasive tests that provide an objective assessment of the functioning of the visual system. With appropriately installed electrodes and specific light stimulation, it is possible to assess the visual system function from the level of the retinal pigment epithelium, individual layers of the retina, optic nerves and the visual pathway to the primary visual cortex. Because clinical electrophysiological testing takes a long time and can be demanding for a patient, it only makes sense with specific clinical indications and with exactly specific tests. The test results are also only useful if we evaluate them in a broader clinical context. The aim of this article is to define all types of electrophysiological tests and to present the indications for referral of patients to eye tests of this kind. The article is based on the guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV) (1) and describes the bases of standard electrophysiological methods, the most common diagnoses and symptoms of the patients, and a presentation of electrophysiological cases from our clinical practice.

## 2 Standard electrophysiological methods for clinical visual testing

ISCEV standards include recommendations for accurate performance of each electrophysiological method, define the recording procedure, electrode placement, calibration of stimulus parameters, data acquisition and analysis of the obtained signal. ISCEV has issued the guidelines for the following electroretinographic methods (Figure 1A): electrooculography (EOG) (2), full-field electroretinography (ffERG) (3), multifocal electroretinography (mfERG) (4), pattern electroretinography, (PERG) (5), and visual evoked potentials (VEP) (6). The methodology is based on observation of light-evoked changes of the electric potential of retinal cells and visual cortex, detected by appropriately placed recording electrodes. In order to record an electroretinogram (ffERG, mfERG and PERG), we place an active electrode on the lower eyelid, and a reference electrode to the skin of the temple on the same side (Figure 1B). There are several types of active ERG electrodes. In Slovenia, we have developed our own non-invasive HK-loop electrode, one of three non-corneal electrodes, defined by ISCEV standards and used internationally (7). EOG is recorded by applying the active electrode and the reference skin electrode on the outer and inner corners of the eye (8). To record VEP (Figure 1C), active silver-chloride electrodes are placed above the primary visual cortex of the occipital lobe, and the reference electrode frontally (9). Besides the electrical activities of the visual system structures, the electrodes also record a series of other bioelectric activities, from brain and muscular activity, to environmental noise. Reliable ERG and VEP measurements require repeated stimulation and signal averaging over time, whereby the repeating electrical response of the visual system structures is isolated from the random environmental noise. Below are descriptions of the physiological origin of responses and the clinical usefulness of the listed standard methods.

### 2.1 Electrooculography (EOG)

Electrooculography is a method for testing the functional integrity of the retinal pigment epithelium (RPE) and its interaction with photoreceptors (2). During the test, the patient moves their eyeballs at a 30-degree angle to the right and left, first for 15 minutes in the dark, then for 15 minutes in the light. At every eyeball

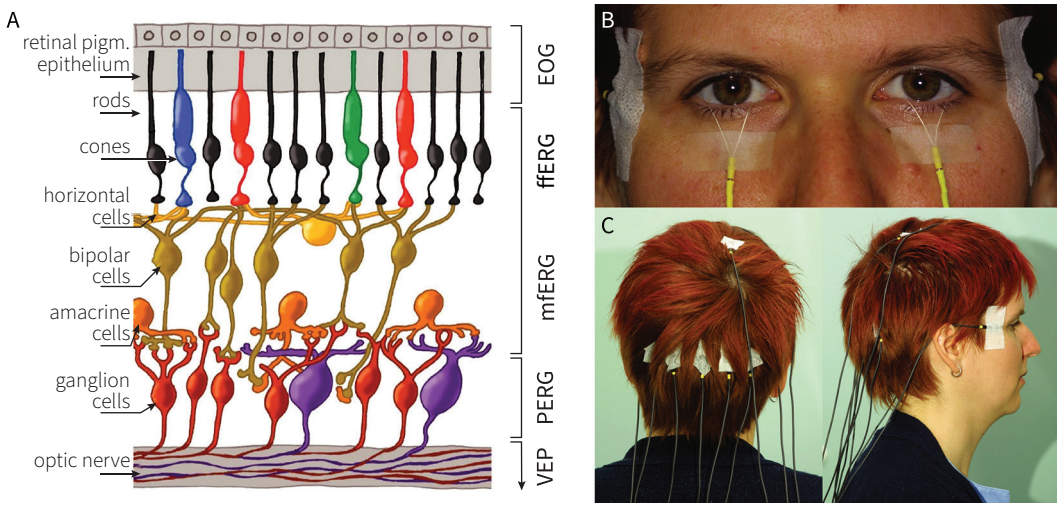


**Figure 1:** A – Standard electrophysiological methods used for clinical diagnostics and layers of the retina or the visual system they belong to. B – Placement of the recording HK electrodes for recording an electroretinogram (ffERG, PERG, mfERG). C – Placement of the electrodes for recording VEP (photographs: Barbara Klemenc; Figure of the retina adapted from webvision.com).

movement, electrodes record the so-called saccade, i.e., the difference in the dipole between the front and the back part of the eye. This difference, also called the resting potential of the eye, is the result of the difference in the voltage between the apical and basal membranes of the RPE. It depends on the metabolic activities between the retinal pigment epithelium and the photoreceptors. Because of the mechanisms that are still not completely understood, the resting potential of the eye, and thereby also the amplitude of the saccade, are lower in the dark and higher in light. The ratio between the highest potential in the light and the lowest potential in the dark is called the Arden index, and with normal RPE it is approximately 175% or higher. The resting potential of the eye does not only depend on the normal activity of the RPE, but also demands a normally functional photoreceptor layer. Therefore, it is not possible to selectively evaluate RPE activity with an EOG test if the activity of the photoreceptor layer is also significantly impaired, which is fairly frequent. EOG is therefore not performed routinely for all retinal dystrophies. Arden index is significantly decreased with the Best vitelliform macular dystrophy (BVMD), where ffERG responses are generally normal (8).

## 2.2 Full-field electroretinography (ffERG)

The most extensive and most important clinical electroretinographic method is full-field ERG (ffERG) (3). It is based on generalised electric responses of the retina, which are the result of stimulation with a series of light flashes. After a 20-minute adaptation to darkness, we record the response of the rod system under dark-adapted (DA) conditions, and after a 10-minute adaptation to light, this is followed by testing the retinal cone system under light-adapted (LA) conditions. The term full-field indicates that the light stimulus captures the whole retina equally. Recording takes place with dilated pupils, thereby ensuring maximum illumination of the retina and lowering the variability of the response between individuals or individual recordings.

The ISCEV standard for full-field electroretinography (3) defines recording the five responses that test the activity of different layers of the retina (Figure 2). Under dark-adapted (DA) conditions, we record dark-adapted 0.01 ERG (DA 0.01 ERG, rod ERG), dark-adapted 3 ERG (DA 3 ERG, combined rod-cone standard flash ERG) and dark-adapted 3 oscillatory potentials (DA oscillatory potentials). The DA 0.01 ERG is stimulated with a very dim light stimulus (0.01 cd s/m$^2$) on a dark background, which enables selective evaluation of the activity of the layers of the rod system's bipolar cells. With brighter flashes (intensity of 3 cd s/m$^2$, also called standard flashes) under dark-adapted conditions, we stimulate the rod system as well as the cone system, obtaining a combined response of both, also called the DA 3 ERG. This is used for testing the activity of all photoreceptors (negative *a*-wave) and all bipolar cells (positive *b*-wave), from both the rod and the cone systems. Because the human retina consists of 120 million rods and only 6 million cones, the activity of the rod system in this response dominates; therefore, any abnormal activity of the cones, whose density is highest at the macula, is not reflected in the DA 3 ERG. Consequently, the DA 3 ERG especially indicates the damage of the rods, which is manifested as a reduced amplitude of *a*-wave, (and consequently also reduced amplitude of *b*-wave), or damage of the bipolar cells of the rod system, denoted by a reduced amplitude of the *b*-wave. With normal photoreceptor activity and a normal *a*-wave, it forms the characteristic negative ERG waveform. The oscillatory potentials that reflect the activity of the amacrine cells, are also stimulated with a standard flash (3 cd s/m$^2$) under dark-adapted conditions. In order to record them, the signal is filtered with a bandwidth filter which retains the fast oscillations while removing lower frequency components (such as the *a*- and *b* waves).

Recording the light-adapted 3 ERG (LA 3 ERG, standard flash "cone" ERG) and light-adapted 30 Hz flicker ERG (LA 30 Hz ERG) occurs under light-adapted conditions. Both responses are stimulated with a standard flash (3 cd s/m$^2$) on a bright background (luminosity of 30 cd/m$^2$), which inhibits the rod system, thereby allowing selective evaluation of the cone system. With the LA 30 Hz ERG the light flashes are delivered with frequency of 30 Hz, which the rod system cannot follow due to physiological limitations. Along with the bright background, this provides additional selectivity for eliciting the responses of the cone system only. The LA 30 Hz ERG mainly originates from the bipolar cell layer of the cone system, while the LA 3.0 ERG has clearly defined two waves, *a* in *b*. The *a*-wave originates from the cone photoreceptors themselves, however, with a minor contribution of the cone Off-bipolar cells. The *b*-wave is formed similarly to the 30-Hz flicker response by the activity of the cone system's bipolar cells. Besides these five standard responses, the ISCEV society also recommends recording additional responses under the extended protocol. Some of these responses are already standardised, e.g. dark-adapted strong flash ERG for a more detailed determination of the rod system function (3), the On-Off ERG for selective determination of the function of the cone On- and Off-bipolar cells (10), the photopic negative response for determining the ganglion cell function (11), and the dark-adapted red flash ERG for determining the cone system function under dark-adapted conditions (12). Some responses, for example the S-cone ERG for determining the short-wave cone system function, are still in standardisation phase; however, clinically they are already in use in our laboratory (13).

ffERG evaluates generalised disorders of the retina and it determines whether the rod system or the cone system is more affected, or whether they both are. It also supports determining the level of damage

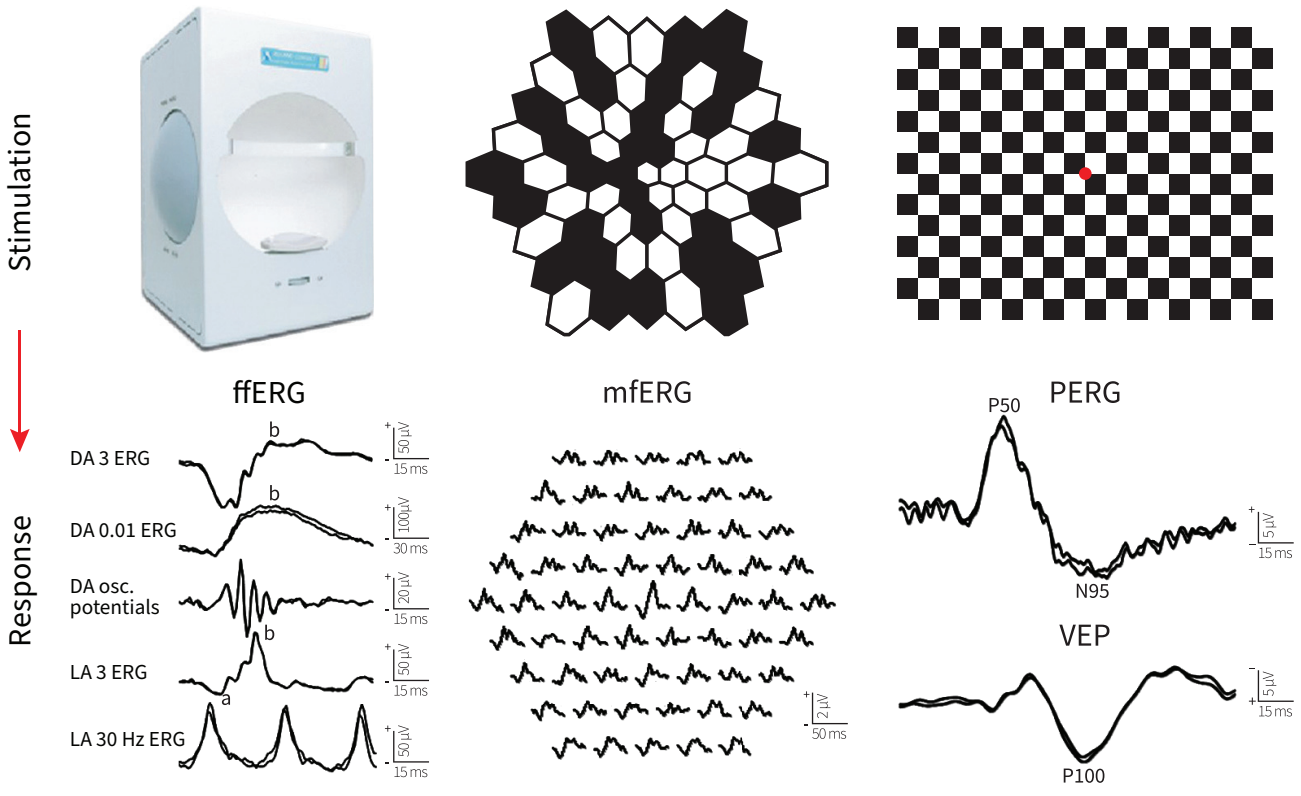


**Figure 2:** Types of the stimulation and the electrophysiological responses of a healthy test subject. The ffERG is recorded in the dome or integrating sphere to ensure uniform light conditions. mfERG, PERG and VEP tests take place with pattern stimulation; the stimulus is displayed on the monitor.

to the retina (photoreceptors or bipolar cells). It should also be mentioned that ffERG evaluates merely the function of peripheral retina, while for the evaluation of the macular function, other electrophysiological methods are used, such as multifocal and pattern electroretinography, which are presented below. Both methods differ from ffERG by the stimulation method, by using pattern stimulus the central retina is stimulated only (Figure 2).

### 2.2.1 Multifocal ERG (mfERG)

Multifocal ERG (4) evaluates the cone system function in the central 30-degree area of the retina. The stimulus consists of several hexagonal fields, and their illumination is repeated in pseudorandom sequence over a longer period of stimulation. The stimulation fields are smaller in the centre and bigger towards the periphery, which fits the different size of retina's receptive fields, and stimulates equally high responses across all areas. The recording electrode records the response with every stimulation pattern change. However, because the sequence of the simulation over time is known, the algorithm is able to subsequently calculate the local response for every stimulation field. This is a mathematically created response, and not a native response that we can obtain with other electrophysiological methods. Local responses consist of two components: from negative N1 and from positive P1. The first originates from photoreceptors and bipolar cells of the cone system, while the second originates only from bipolar cells of the cone system. This is a similar response to the LA 3 ERG with ffERG; however, it is presented as localised responses in the central 30-degree area of

the retina. This allows topographic evaluation of the function of individual smaller areas of the central retina and identification of dysfunction of photoreceptors in the macula in a very early phase, which is especially important when diagnosing maculopathy. In combination with ffERG, it is therefore possible to evaluate whether a patient has a generalised or merely macular impairment of the retina, or if he has preseved macular function and abnomality of peripheral retina only. Since mfERG does not reflect the activity of ganglion cells, the combination with PERG recording evaluates whether this is an impairment of the outer or inner layers of the central retina.

### 2.2.2 Pattern ERG (PERG)

PERG (5) enables evaluation of the macular function and the function of the ganglion cells of the central retina. It can be stimulated with a high-contrast black and white reversing checkerboard stimulus. The response consists of two components. The P50 positive wave reflects activity of both macular bipolar cells and ganglion cells, so it evaluates the function of the macula. The N95 negative wave originates exclusively from ganglion cells, therefore it evaluates the function of the ganglion layers of the retina. In combination with other tests, pattern ERG becomes a significant tool for discovering the level of the impairment. When there is a question of retinal dysfunction, we can subsequently record ffERG and PERG to determine whether there is a macular impairment, when only PERG is affected, or a generalised retinal impairment, when both PERG and ffERG are usually affected. If there is a question of unexplained vision loss, simultaneously recording of PERG and VEP helps us to define whether loss of sight is the result of maculopathy or neuropathy or a cortical impairment or (if the responses are normal) there could be possible inorganic causes. It should be emphasised that inappropriate refraction, the lack of translucency of optical media or poor fixation of the patient, can significantly affect the pattern ERG. Consequently, response evaluation is only possible under appropriate recoding conditions.

### 2.2.3 Visual evoked potentials (VEP)

In order to assess the function of optic nerves and the visual pathway to the primary visual cortex, we use the VEP test (6). According to ISCEV standards for recording, either pattern reversal or pattern onset is used. The first, i.e., pattern reversal stimulation, is the most sensitive for discovering an impairment in the conduction along the visual pathway. The component we measure during this process is the P100, i.e., the positive wave, which has a latency of approximately 100 ms. The amplitude, latency and shape of the P100 wave tells us whether conduction has been delayed (prolonged latency) or blocked (lower amplitude), or both at the same time. The formation of the P100 wave additionally tells whether this includes only the fibres originating from the macular area. If we place several recoding electrodes on the occipital lobe of the visual cortex (i.e., the multichannel VEP, an upgrade of the standard ISCEV protocol) and use different types of stimulation (full-field and half-field) we can also determine the location of the impairment in the visual pathway (optic nerve, chiasm, retrochiasmal visual pathway or visual cortex). However, in order to make a reliable evaluation of the conduction along the visual pathway, we also need the information about the preservation of the retinal function, so we record PERG alongside VEP, using the same stimulus.

Besides the above-described pattern-reversal stimulation, we also use the pattern-onset stimulation and flash stimulation. These two methods of recording VEP are used especially when stimulation with the standard reversal stimulus is not possible, e.g., with unstable fixation due to nystagmus or with poorer patient

cooperation. Onset VEP is useful for assessing the preservation of the visual function in small children. Flash VEP is useful for evaluating the integrity of the visual pathway with established blurred optic media. It is also useful for evaluating the level of incorrect visual system function with unexplained severe or total vision loss. Besides the above tests, we also record multifocal VEP for research purposes (14). This is a new technique, not yet standardised globally, but it does support identification of localised dysfunctions of the optic nerve and the visual pathway. The limiting factor for more extensive clinical use is the high variability of the mfVEP response in normal population.

## 3 Clinical indications for referrals to visual electrophysiology

We describe the most frequent diseases, symptoms and clinical questions with which it is sensible to utilise electrophysiological tests, with added cases from our electrophysiological practice. Table 1 lists the most frequent reasons for referrals, as well as the selection of the most sensible method for resolving the clinical question. It has to be emphasised that electrophysiological tests are long and demanding. Consequently, the patient's tiredness (and thereby their poorer cooperation) can have a significant impact on the results. Therefore, it is sensible to perform targeted tests that provide the key information to the posed clinical question on the function of a certain part of the visual system. It is only sensible to perform additional electrophysiological test when findings are still unclear. However, all established electrophysiological abnormalities should always be compared to other clinical findings and morphological and functional tests.

Every year, between 600 and 700 patients are referred to electrophysiological tests at the Unit for visual electrophysiological diagnostics of the Department of Ophthalmology, University Medical Centre Ljubljana, most often by specialists in retinal disease, neuro-ophthalmology and paediatric ophthalmology, as well as regional ophthalmologists, neurologists and other specialists. More than a half of treated patients are preschool or school

**Table 1:** The list of the most frequent indications for electrophysiological testing and used electrophysiological methods (summary from 1 and 15). This is a simplified chart of using electrophysiological methods; a more detailed chart and the most important referral diagnoses is available in international guidelines (1).

| Clinical question | EOG | ffERG | mfERG | PERG | VEP |
|---|---|---|---|---|---|
| Dystrophies and other retinal impairments | × | + | + | + | |
| Optic neuropathy, intracranial changes | | | | + | + |
| Unexplained impairments or loss of sight | | + | + | + | + |
| Toxic and nutritional eye diseases | | + | + | + | + |
| Assessment of the electrophysiological visual system function in a child | | +* | | | +* |
| Nystagmus | | + | | | +* |

\+ The most indicated test.
× Test added when Best dystrophy is suspected.
* Special version of the test (explained below).

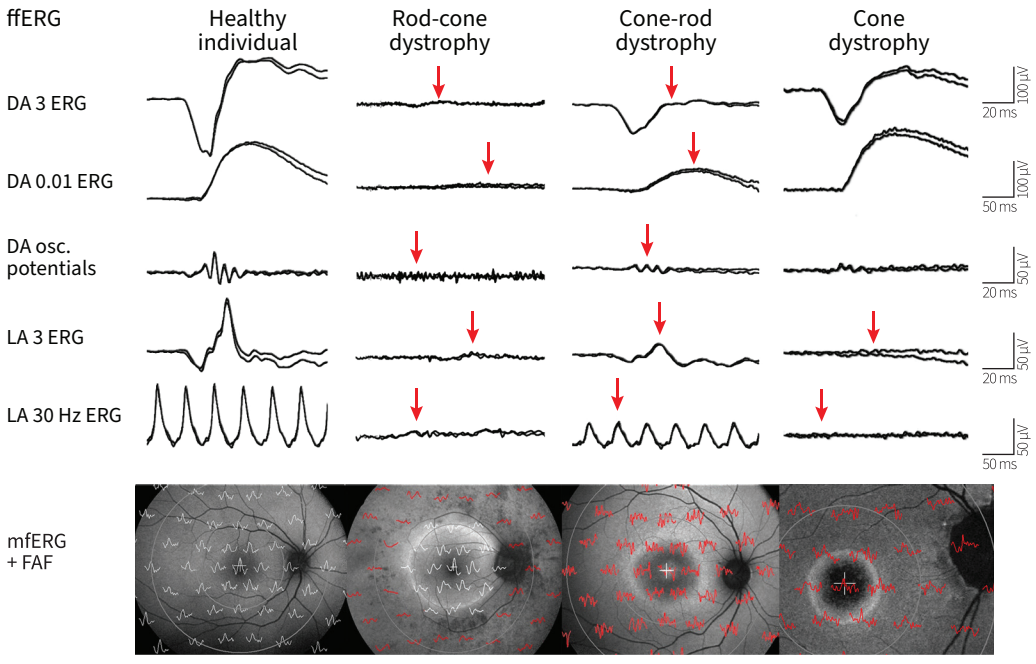


**Figure 3:** The ffERG and mfERG results (super-positioned on the image of fundus autofluorescence – FAF) in a patient with rod-cone dystrophy (the depicted case has advanced form of pigment retinopathy), a patient with cone-rod dystrophy and a patient with cone dystrophy. Electrophysiological findings were bilaterally symmetric, the right eyes are shown. With rod-cone dystrophy, a severe loss of peripheral rod and cone function with preserved cone function in the macula is noticed (absence of the response of the rod system and severely reduced responses of the cone system with ffERG, while mfERG is normally preserved in the macula). With cone-rod dystrophy the pattern is reversed: there is an abnormal macular function, while the peripheral retinal function is preserved, but reduced (abnormal mfERG, reduced ffERG). With cone dystrophy the rod system responses are normal, while the responses of the cones of the peripheral and central retina are abnormal (normal response of rods, absent response of cones with ffERG and abnormal mfERG).

children. They are most often referred as part of diagnosing congenital nystagmus and early retinal diseases, and for assessing the visual system function with high-risk neurological symptoms. Children with amblyopia that is not improving even with appropriate optical correction and orthoptic exercises are also frequently referred. Adult patients are most often referred because of diagnosed neuropathy and intracranial reasons for sight impairment (approximately 20% of referrals). These are followed by referrals following a diagnosis of a retinal disease (approximately 15%) and due to unexplained vision impairment (also 15%). Referrals for excluding toxic and nutritive eye diseases are less frequent (up to 5%), and there are also some other reasons for referrals that are more difficult to classify in the above diagram.

## 3.1 Dystrophies and other retinal impairments

Retinal dystrophies are certainly the most frequent reason of referral for electrophysiological testing. Tests that we conduct with such a referral diagnosis are ffERG for determining the rod system and cone system function, and the possibility of a generalised retinal impairment, and

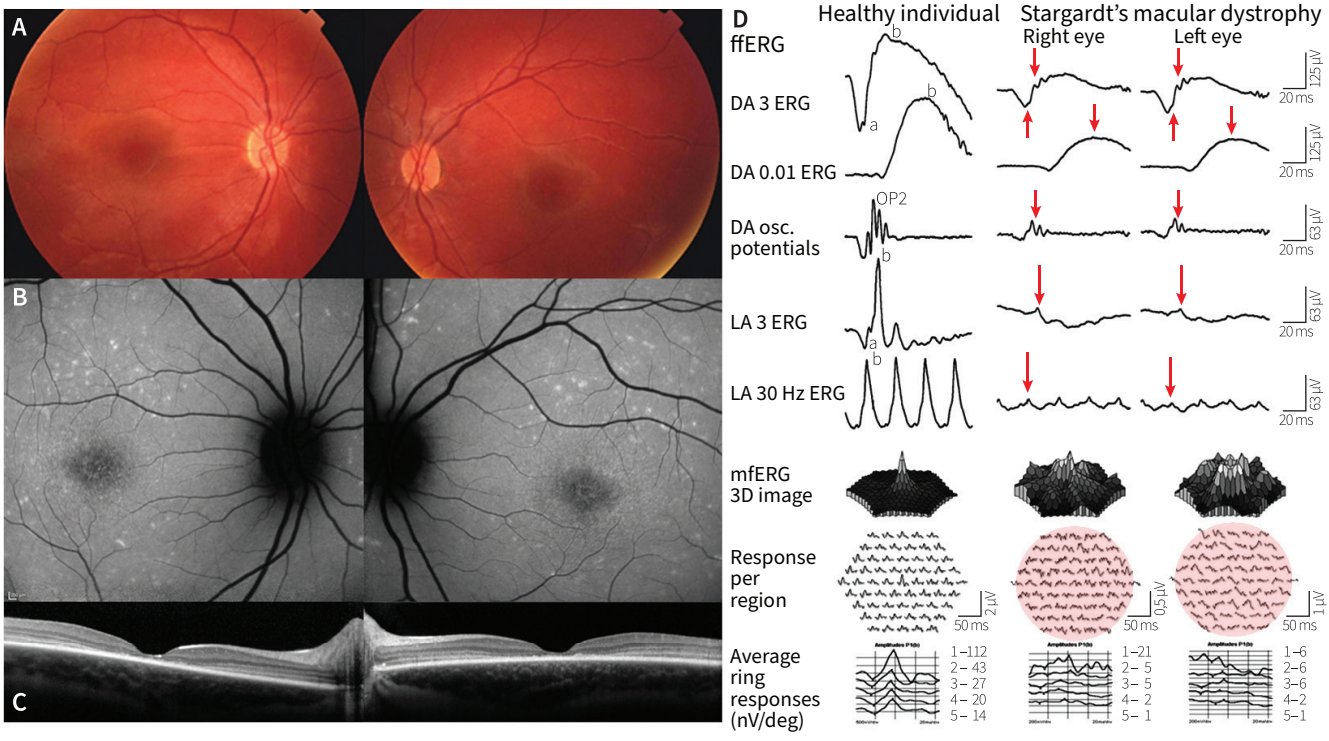


**Figure 4:** Image of the fundus (A), image of fundus autofluorescence (B), optic coherent tomography (OCT) of the macula (C), and the results of electrophysiological tests (D) for an 8-year-old girl with a genetically confirmed Stargardt disease, also present in her older sister. Electrophysiological result has shown the impairment of the rods and cones of the peripheral retinal function (abnormal DA and LA responses with ffERG), and the impairment of the macular function (abnormal mfERG), which was present already in the early phase, indicating a case of fast-progressing Stargardt disease.

mfERG and/or PERG for determining macular impairment. This allows us to distinguish whether the case is a macular dystrophy or a generalised dystrophy of the photoreceptors (Figure 3). With the latter, we can distinguish characteristic subtypes of retinal dystrophy with either an impairment of rods or cones, or a mixed impairment of both types of photoreceptors in different proportions. Figure 3 depicts a few types of dystrophies with which either rods or cones are more impaired, which can often not be clearly delimited clinically. Conducting electrophysiological tests is sensible in such cases, as it determines whether this is a dominating disease of the cone system or the rod system, while electrophysiology objectively determines the level of dysfunction of the retina. One of the most frequently referred types of hereditary retinal dystrophies is pigment retinopathy (RP), with which impairment of the rod system is characteristic for its early phase, while the cone and macular function are preserved. With an advanced form of RP (as depicted in Figure 3), we typically notice the absence of the response from both the rod and the cone systems. The macular response (mfERG and PERG) is, however, preserved in the proportion of the preservation of the central visual field. With hereditary retinal dystrophies, it is sometimes sensible to conduct electrophysiological testing of the patient's family members who have vision issues, even when the fundus does not yet show any clear clinical signs.

Electrophysiological determination of patients with the Stargardt disease is also important, as the electrophysiological

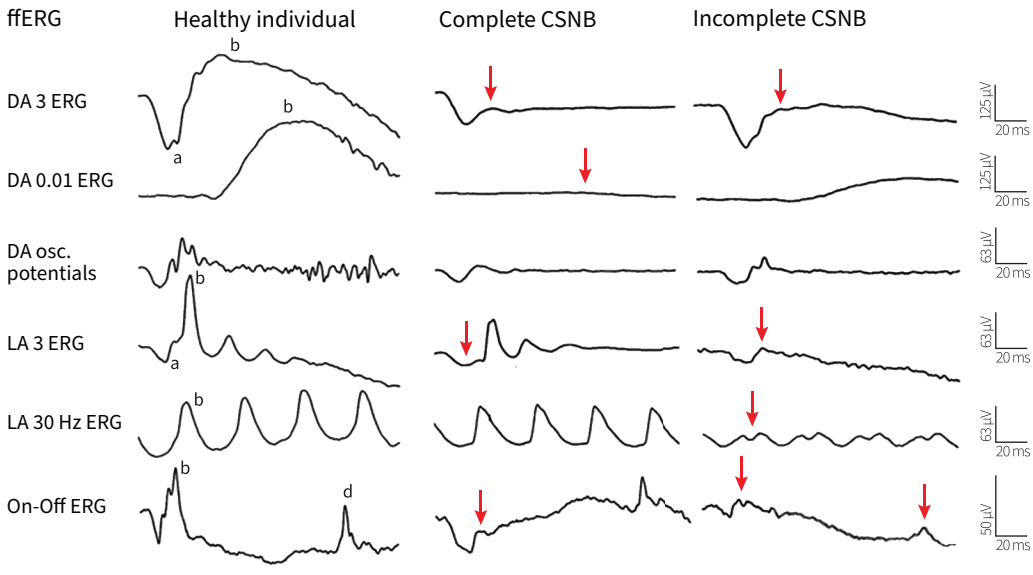


**Figure 5:** Typical ffERG changes with complete and incomplete congenital stationary night blindness. Both types manifest a characteristic electronegative waveform of the DA 3 ERG, which depicts normal photoreceptor function and an impairment of the bipolar cell function. For the complete CSNB, which shows a total impairment of On-bipolar cells, the DA 0.01 ERG is completely absent, as the On-type rod bipolar cells do not function. The LA 3 ERG and LA 30 Hz ERG are preserved, but slightly altered, because the contribution of the On-bipolar cells is missing, while the contribution of the Off-bipolar cells is preserved. This change is more evident when recording On-Off ERG, where the On-bipolar cell component is completely absent (*b*-wave), while the Off-bipolar cell component is normal (*d*-wave). With the incomplete congenital stationary night blindness both types of bipolar cells are partially impaired. This is manifested as a present, yet reduced DA 0.01 ERG, with the LA 3 ERG and LA 30 Hz ERG reduced, while with On-Off ERG both *b*- and *d*-waves are reduced, pointing to an impairment of both On- and Off-bipolar cell function.

findings determine the level of the impairment and provides the information on the progression of the disease (Figure 4). In electrophysiological terms, we differentiate between three phenotypes of Stargardt disease (16): type 1, where only the macular function is impaired (abnormal mfERG and PERG, normal ffERG), type 2, where the macular function is impaired and there is a generalised abnormality of cone function (abnormal mfERG and PERG, abnormal LA ERG, normal DA ERG), and the fast progressing type 3, with a generalized impairment of both the macula and the cones and rods of the peripheral retina (abnormal ffERG, mfERG and PERG). With patients with vitelliform macular dystrophy it is also important to exclude Best vitelliform macular dystrophy (8,17). An important electrophysiological characteristic of Best vitelliform macular dystrophy is abnormal retinal pigment epithelium function, which is reflected in an abnormal EOG. It is important to note that an abnormal EOG is present in all phases of the disease, even before the vitelliform change is expressed on the fundus. Considering the autosomal dominant inheritance of the gene, EOG testing makes possible to discover affected family members even before the disease is expressed. There are also other forms of vitelliform and pseudo-vitelliform degenerations that are not carried over through autosomal dominance. With those, EOG is not necessarily abnormal (18).

With certain types of retinal dystrophies, the electrophysiological changes are so specific that an electroretinography not only determines the type of retinal dystrophy, but even the gene responsible for the development of the disease. This are so-called pathognomonic electrophysiological alterations, which have been so far only described for three congenial retinal disease: cone dystrophy with supernormal DA ERG, caused by a mutation in the KCNV2 gene, enhanced S-cone syndrome, (ESCS) with a NR2E3 mutation, and bradyopsia with the mutated gene RGS9/R9AP (19). With ESCS, it is essential to record additional ERG responses according to the extended protocol, along with a ffERG test. If the retina is stimulated with a blue stimulus on a yellow background, we can selectively provoke the S-cone system. This is the so-called S-cone ERG, which is abnormally increased with ESCS because of the excessive activity of the S-cone system with this disease (20).

Besides the progressive types of retinal dystrophies, a patient's vision might also be impaired as a result of stationary retinal disease. In patients with normal fundus and difficulties with night vision, the electrophysiological test should exclude congenital stationary night blindness (CSNB). In electrophysiological terms, we differentiate between an autosomal recessive and X-linked types. This is the so-called Schubert-Bornschein type of CSNB, which is characteristic with an electro-negative type of ERG response, demonstrating an impairment of the retinal bipolar cells (Figure 5). This can be further differentiated into complete and incomplete types of the Schubert-Borschein type of CSNB (21). For the complete CSNB type, it is characteristic that On-bipolar retinal cells do not function, while for the incomplete type, both On- and Off-bipolar cells function only partially. In order to distinguish between the complete and incomplete CSNB, an On-Off ERG recording must be made in order to determine whether the impairment of On-bipolar cells is complete or whether there is a partial impairment of both types of bipolar cells. We also distinguish the autosomal dominant CSNB, also called Riggs-type CSNB. Its characteristic is a complete absence of rod activity and related structures, while the cone system functions normally. A congenial stationary disease with characteristic photophobia is achromatopsia. A ffERG recording shows characteristic changes with normal rod system function and a severe cone system dysfunction (absence of the LA responses). If we include recording the S-cone ERG we can also exclude the possibility of the S-cone monochromatism. It is characterised by normal DA responses and the attenuation of LA response; unlike with achromatopsia, this type of retinal disease has retained a normal response of the S-cone system (22).

## 3.2 Optic neuropathies, intracranial changes

If retinal impairment is not the cause of decreased vision, testing with electrophysiological methods is important, especially if there is no apparent abnormality in the fundus and vision loss has not been clinically explained. Even with OCT and neuroradiological diagnostics, the visual pathway function can only be assessed objectively using electrophysiological methods. The pattern of VEP changes in combination with PERG or mfERG can differentiate between abnormal conduction along the optic pathway, from maculopathy even before the changes are visible in the imaging tests, and it also determines the level of conduction abnormality along the optic nerve, the chiasmal area and the retrochiasmal visual pathway.

A frequent reason for clinical referral to VEP is a suspected optic neuritis. It is clinically manifested as an acute loss of visual acuity with a pain when moving the eyeball. The typical VEP changes show delayed VEP P100 latencies, which persists

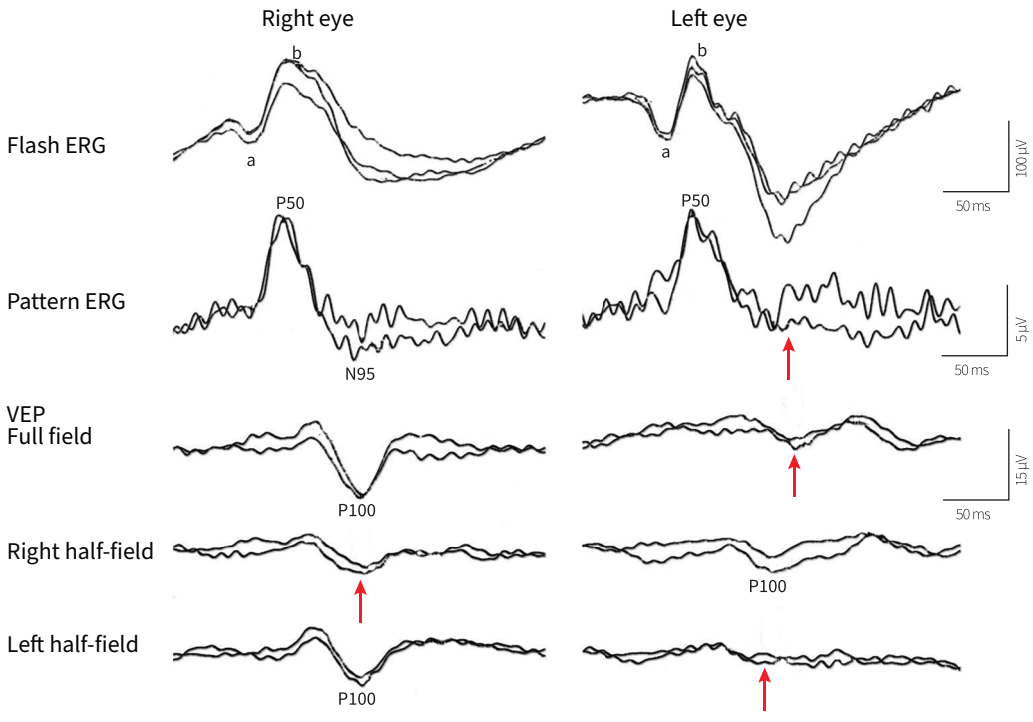


**Figure 6:** The case of a patient who was hospitalised with atrophy of the optic nerve on the left eye. He accidentally noticed the visual impairment, when he covered his right eye, which had no symptoms. Along with the atrophy of the left optic nerve, there was an anormal function of the ganglion cell axons seen as a reduced N95 wave on the PERG. On this eye, the VEP P100 for the full-field stimulation was reduced and moderately delayed, when compared with the right eye, which pointed to a partial block of conduction along the optic nerve of this eye. At the same time, both eyes manifested a partial block along crossed fibres of the optic nerve, manifested as relative reduction on the right eye, when stimulated with a right half-field, while on the left eye there was a reduction with left half-field stimulation (red arrows indicate abnormal P100). The MRI of the head, which the patient undertook later, showed a pituitary adenoma of the left optic nerve and the optic chiasm.

also after the visual acuity returns, and a significant reduction in the P100 amplitude at the acute phase of the disease. The role of electrophysiology in diagnosing an optic neuritis is objectivization of functional abnormality already in the acute phase for assessing the magnitude of the conductional block along the optic nerve. After the acute stage, the electrophysiological assessment is especially important if the expected improvement of visual acuity does not occur, to evaluate the impairment of the optic nerve as the result of demyelisation or axonal damage, and for monitoring remyelination (23). When visual acuity does not begin to improve after the acute recovery phase, which is characteristic for atypical forms, related to axonal damage (e.g., with neuromyelitis optica (NMO) or with Leber's hereditary optic neuropathy (LHON)), electrophysiology evaluates the loss of optic nerve fibres and the degeneration of ganglion cell axons. This is shown as a reduced N95 wave of the PERG (1,23). Prolonged VEP P100 latencies can also be present in asymptomatic patients with multiple sclerosis, where the VEP indicates a subclinical demyelisation of the optic nerve (1).

Sudden and irreversible loss of vision, not accompanied by pain, is characteristic of non-arteritic anterior ischemic optic

neuropathy (NAION). If visual acuity is retained, the VEP changes are shown as a reduction in the amplitude without major abnormality of the response latency. With arteritic anterior ischemic optic neuropathy (AAION), loss of vision is usually more severe. Accordingly, VEP is also more abnormal, and therefore with typical ischemic optic neuropathies, electrophysiological testing does not provide any additional information (1).

Leber's hereditary optic neuropathy (LHON) is generally manifested as a consecutive bilateral loss of visual acuity with reduced colour vision, central scotoma and hyperaemic papillae, usually without leakage of dye on papillae with fluorescent angiography. A typical electrophysiological abnormality can already be present in the acute phase of the disease, and can be manifested as a rreduced N95 wave of the PERG and P100 wave of the VEP, indicating a predominant dysfunction of retinal ganglion cells and subsequent degeneration of the optic nerve fibres (24).

Neuroradiology examinations are certainly the most important diagnostic procedures for compressive optic neuropathies. However, due to progressive loss of vision without any explicit morphological signs of worsening patients require electrophysiological tests to objectivise the progression. This is also important with more severe forms of thyroid-associated orbitopathy, where the neuroradiology assessment of the compressive optic neuropathy is hindered. A detailed electrophysiological determination of the abnormality requires recording of a multi-channel VEP, which has become standard in most electrophysiological laboratories in Slovenia, even though it is not required by the ISCEV standard (6). When a tumour affects the optic nerve of only one eye and does not touch chiasm, we notice an electrophysiological reduction of the VEP amplitude and a partial delay in the latency of the VEP response in this eye. However, these changes cannot be differentiated from other causes of neuropathy. When the chiasm is also affected, we notice characteristic abnormality, called crossed asymmetry. This means that the abnormality of the right eye is manifested with abnormal VEP P100 to full-field stimulation above the right hemisphere of the brain, and vice-versa - the VEP from the left eye is abnormal above the left hemisphere. Such abnormalities are even more clearly captured with half-field stimulation, for which a VEP abnormality to the temporal half-field stimulation is characteristic (it is used to stimulate the crossed fibres of the optic nerve), while the signal is normal for the stimulation with the nasal half-field. Figure 6 shows an example of a patient with such a pattern of change. Incorrect conduction along the retrochiasmal visual pathway causes uncrossed asymmetry, with which the VEP response from both eyes is abnormal above the same hemisphere (1,23).

Characteristic electrophysiological changes are also present with glaucomatous optic neuropathy, where the reduced PERG is the result of deteriorating ganglion cells (25). The reduction of the photopic negative response in the early phases of the disease is also characteristic (26), while VEP changes are generally not specific until late stages of the disease because of the preservation of the central field of vision. Therefore, referring glaucoma patients to electrophysiological testing is only sensible when their loss of vision can not be explained by clinical findings.

## 3.3 Unexplained visual loss

When the cause of vision loss cannot be explained, referring a patient to electrophysiological tests is certainly important, as subjective claims of eyesight deterioration do not match the clinical presentation. The reasons for such derogations can be different; there could be intracranial causes for vision impairment, it could be an early stage of an impairment not yet

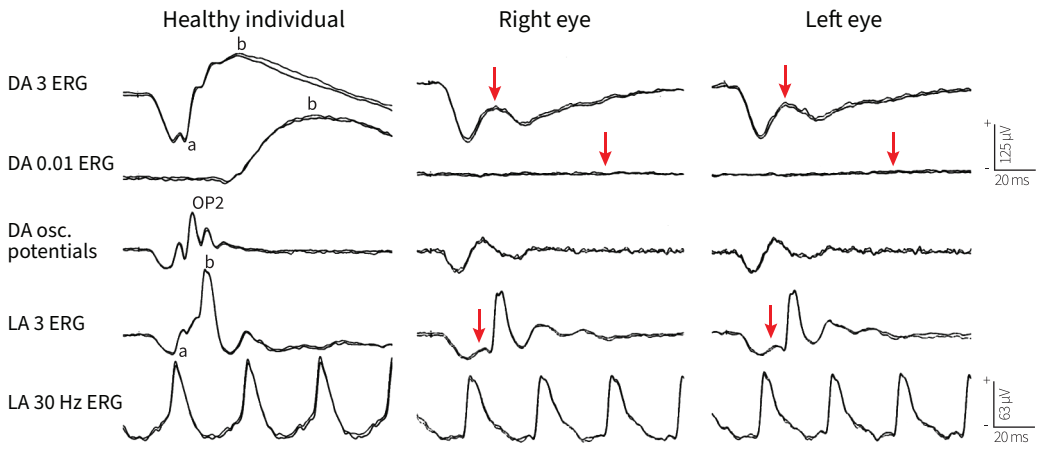


**Figure 7:** The case of unexplained constriction of visual field and impairment of night vision with a 31-year-old patient. The ffERG results showed an electronegative DA 3 ERG, while the *a*-wave was normal, and *b*-wave significantly reduced below the baseline. The DA 0.01 ERG was not recordable and individual oscillatory potentials did not form. The LA 3 ERG had a significantly altered waveform – broadened *a*-wave and a sharpened *b*-wave pointed to a missing component of On-bipolar cone system cells, while the values of the LA 30 Hz ERG were within normal.

morphologically manifested on the fundus (a functional impairment frequently occurs before the morphological impairment), and sometimes there are inorganic causes. It should be mentioned that a normal result with unexplained vision impairment still does not mean that the patient's vision loss is malingered. Tests capture the visual system function only up to the primary visual cortex; however, interpreting visual information is the task of complex brain processes, and a normal electrophysiological result does preclude their impairment.

The significance of electrophysiology in diagnosing unexplained visual loss is to define at the level of impairment. The most frequent unexplained impairment is loss of visual acuity, with an electrophysiological distinction between abnormal macular function and an optic nerve impairment. A frequent indication for referral is also loss of visual field. With a concentric loss of the visual field we can confirm retinal impairment such as pigment retinopathy. In some cases, the changes can reveal an impairment of a specific cellular type in the retina or the visual pathway, as shown in the two cases below.

### 3.3.1 The case of unexplained constriction of visual field and impairment of night vision

A 31-year-old woman was referred to an electrophysiological test for unexplained vision impairment. A few months before the test, she had a gynaecological procedure under general anaesthesia, after which she began to notice flickering along her whole field of vision, she had more problems at night or with poor light conditions. She had no issues with her vision priorly. Upon the clinical examination, her visual acuity was 1.0, bilaterally, along with a concentric constriction of visual field on both eyes. There were no other clinical abnormality that could explain the vision impairment. She underwent a ffERG test (Figure 7), which revealed changes, characteristic of the impairment of the On-bipolar cell function. This was evident from the electronegative waveform of the DA 3 ERG, absent DA 0.01 ERG, and the characteristically altered waveform of the LA

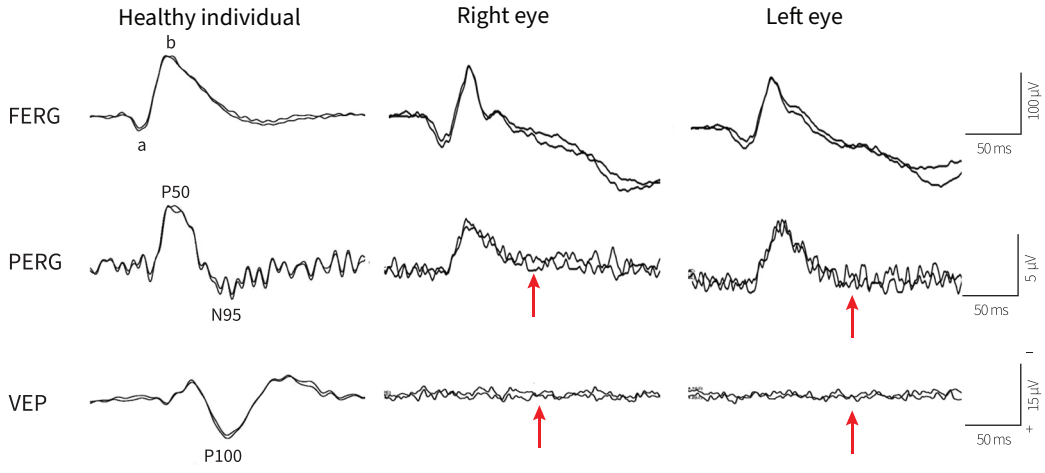


**Figure 8:** The case of a patient with clinically atypical Leber hereditary optic neuropathy. The results of electrophysiological tests on both eyes showed a normal flash ERG and a normal P50 of the pattern ERG, the N95 was raised above the baseline, VEP was not recordable.

3 ERG. Such a pattern of change is characteristic for the complete type of congenital stationary night blindness, or in case of acquired disease, such a condition can coincide with melanoma associated retinopathy (MAR) (27). Based on electrophysiological changes, we referred her to additional clinical diagnostics, but they have not discovered a malignant process so far.

### 3.3.2 The case of unexplained bilateral vision loss

A 57-year-old man was referred to electrophysiological test for unexplained bilateral vision loss. His condition followed a cerebrovascular insult, indicating a possibility of a cortical vision loss. Only a few months after the vision impairment, the patient first saw an ophthalmologist, and during the diagnostics procedure underwent a CT and MRI of the head: there were signs of atrophy after the stroke right occipitally and right in the thalamus (leukoencephalopathy). At the last ophthalmologic examination, he had very low visual acuity (right eye – counting fingers at 1.5 m, left eye – counting fingers at 0.5 m), his macula was normal, while there was a partial pallor of the optic nerve head and partially thinner retinal ganglion cell layer on OCT.

Electrophysiological result (Figure 8) with an abnormal N95 wave of the pattern ERG showed signs of bilateral impairment of ganglion cell function, while a severely abnormal VEP indicated signs of impaired conduction along the optic nerve. This pattern of change showed that this was not cortical impairment, but a bilateral optic neuropathy with ganglion cell damage. Further clinical monitoring showed a progressive atrophy of the optic nerve fibres on OCT. Because of the concurrent electrophysiological signs of the impairment to the ganglion cell function, he was referred to genetic testing for Leber's optic neuropathy. A positive mutation in the mitochondrial genome (11778) was identified.

## 3.4 Toxic and nutritional eye diseases

Referral to electrophysiological tests with the possibility for toxic and nutritive eye diseases is especially important for differentiating whether this is a case of a toxic retinopathy or a toxic optic

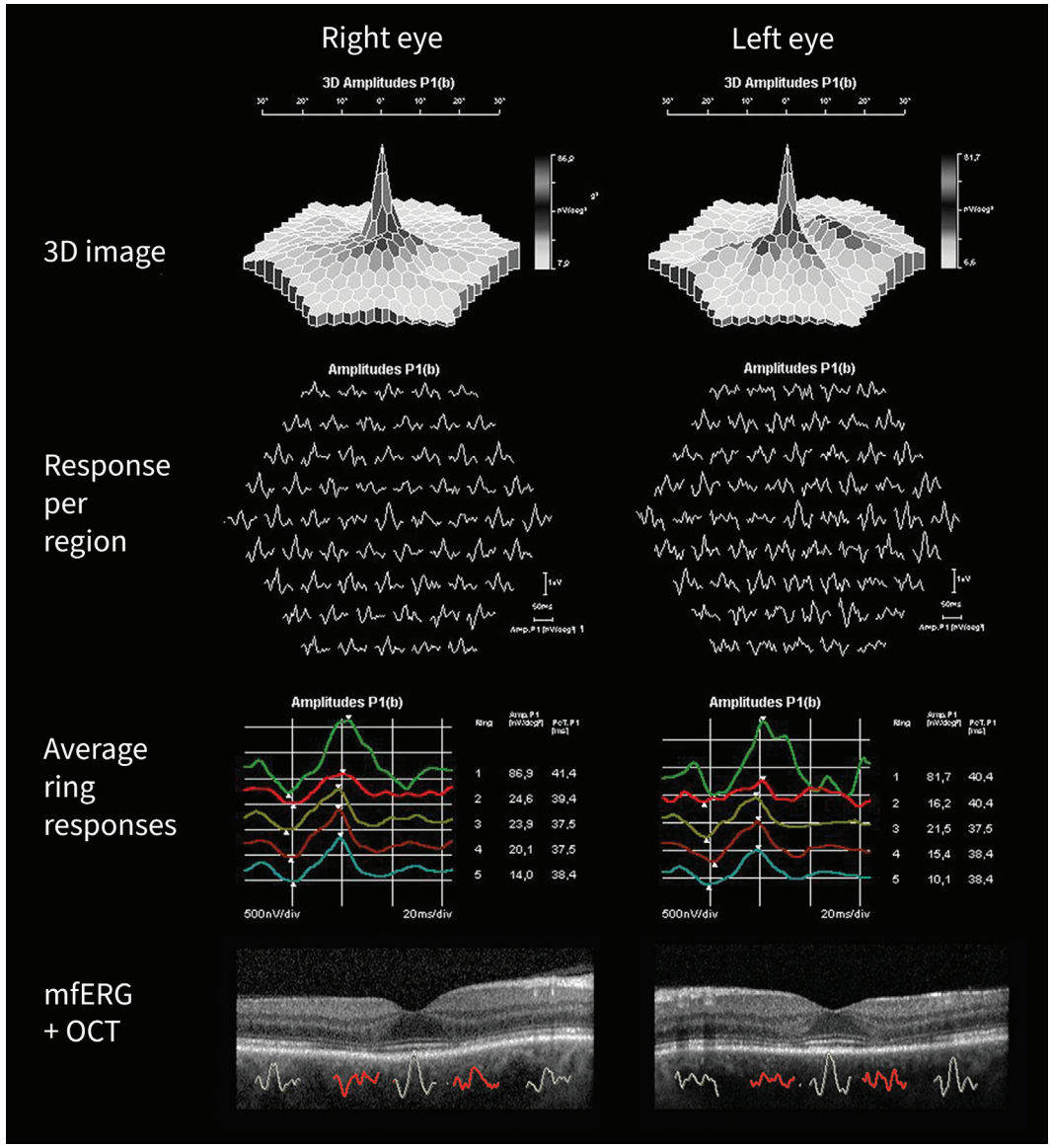


**Figure 9:** The case of a 54-year-old patient who was treated with chloroquine for systemic lupus for 12 years. Subjectively she did not notice any decrease in vision, her visual acuity was normal on both eyes (1.0 with correction), however, on the M2 TOP visual field testing there was a parafoveolar reduction in sensitivity. Multifocal ERG showed a preserved response in the fovea region (the first ring in the average ring responses), and a characteristic parafoveolar reduction (the second ring of the average ring responses). The reduction coincided with a morphology impairment visible with OCT, where the parafoveolar region showed a thinner outer nuclear layer of the retina and the rarification of the IS/OS line.

neuropathy, and to objectively determine the level of the function impairment. The latter is especially important in the early phases of the disease, when the morphological changes are not yet apparent enough, so the retinotoxic process can be misdiagnosed. The patients receiving chloroquine or hydroxychloroquine for treating autoimmune diseases are frequently referred in this regard. Multifocal ERG is one of the most accurate tests for early detection of toxic change on the

retina (28). Since an mfERG test takes a long time and has a similar level of accuracy as spectral optic coherent tomography (SD-OCT), referring all patients who are being treated with chloroquine is not sensible according to international guidelines. However, it is imperative to refer all those suspicious cases, especially when a patient already has a loss in the field of vision, and the morphological change on the retina is not yet apparent. In such early phases of the disease, the typical finding from the multifocal ERG is as follows: reduced signal in the parafoveolar region, as revealed by the second ring of responses from the multifocal ERG (Figure 9). This change is most easily seen by calculating the ratio between the rings, allowing us to determine the relative deviations of the signal in this area. Electrophysiological tests are used to exclude retinotoxicity when the patient is receiving antiepileptic therapy with vigabatrin, breast cancer therapy with tamoxifen, and other less common forms of therapy. Characteristic changes in retinal and optic nerve function may also occur as a result of methyl alcohol poisoning. Retinopathy from vitamin A deficiency can also require electrophysiological testing. The electrophysiological findings that we obtain from this, is the absence of rod activity, similarly to the autosomal dominant congenital stationary night blindness. Sometimes the deficiency of a certain substance can impair the optic nerve function, which is characteristic for nutritional optic neuropathy resulting from vitamin B12 deficiency. Toxic aetiology of optic neuropathy can also be the result of ethambutol, and in rare cases also of tobacco toxicity or as a result of treatment of the arrhythmia with amiodarone (1).

## 3.5 Assessing electrophysiological visual system function in a child

One of the most important parts of electrophysiology is the assessment of a child's visual system. Because the tests are non-invasive and objective, they can be used to assess the visual system function, while also providing indirect information on the quality of visual development. This is especially important for newborns and small children with risk factors or with children who cannot yet perform psychophysical tests for assessing the visual system function, because they do not speak yet (Figure 10). Because of potentially poor cooperation, electrophysiological recording of children requires customized methods and trained staff (in Slovenia paediatric electrophysiology is performed according to the so-called GOSH protocol, which was implemented in cooperation with the London Great Ormond Street Hospital). ISCEV standards for pediatric electrophysiology are in development (29,30). The GOSH protocol for recording small children is described in detail elsewhere (31), while ISCEV-standard-based tests can be performed with children from 7 years of age, i.e., when they are able to appropriately cooperate in tests. Testing early in a child's development can help identify the cause of poor visual contact. With suspected retinal dystrophy or its impaired function, the specific pattern of flash ERG abnormality can help to distinguish different types of retinal diseases and helps to determine the extent of retinal damage. With suspected impairment of conduction along the optic nerve or visual pathway, characteristic VEP changes can differentiate between certain types of congenital and acquired impairment of optic nerve or visual pathway function. In amblyopic children, electrophysiological testing can determine the reason why the eye has not been responding to therapy even with orthoptic exercises and regularly covered unaffected eye. With older children, visual electrophysiology can be useful in diagnosing the causes of headache, and with suspected inorganic

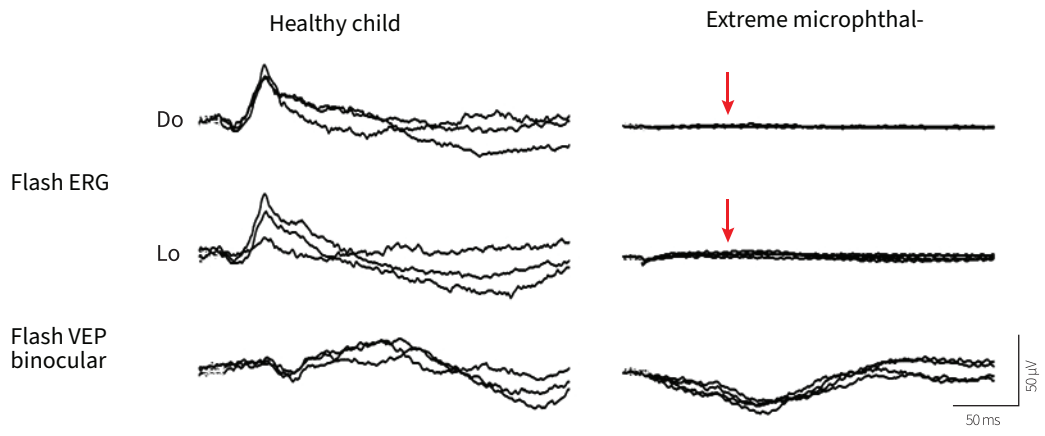


**Figure 10:** The case of a 10-year-old boy who was referred to electrophysiological tests to determine the preservation of visual system function with the extreme microphthalmos and poorly recognised optic structures. There was no measurable ERG response from the retina, while the VEP response to flash stimulation above the visual cortex was still preserved, showing that he detects light.

causes of vision loss or with toxic effects of certain drugs, e.g., vigabatrin.

## 3.6 Nystagmus

The importance of electrophysiological tests in diagnosing nystagmus is described in more detail elsewhere (32). Considering the pattern of electrophysiological changes, we can briefly determine whether this is an idiopathic, sensory or neurological nystagmus. With a normal clinical and electrophysiological findings, we can conclude it is a case of congenital idiopathic nystagmus. When there are changes to ERG and/or VEP, we speak of sensory causes for congenital nystagmus. When a retinal impairment is identified, the changes to ERG can be specific enough to differentiate different types of retinal dystrophy and other retinal impairments. The most frequent reasons are Leber congenital amaurosis, congenital stationary night blindness and achromatopsia (33). When we detect an altered VEP with a normal ERG, we speak of postretinal causes of sensory nystagmus. These include optic nerve hypoplasia, ocular albinism and achiasmia (34). Neurological nystagmus occurs in the scope of neurological diseases, in connection with chromosomal impairments and certain syndromes. In case of acquired nystagmus as a consequence of a neurological disorder, it is also important to perform an objective assessment of the visual system, especially electrophysiological testing with VEP. This excludes potential pathology along the visual pathway due to compressive changes, demyelinating diseases and other causes (35). It must be mentioned that diagnosing causes for nystagmus, regardless of whether the patient is a child or an adult, requires customized testing protocol. Patients with nystagmus are not capable of an appropriate fixation of the stimulus, therefore tests using mfERG, PERG and pattern-reversal VEP can no longer be performed. For these patients, the retinal function can only be determined with a ffERG test (or with very small children with a customised protocol of flash ERG, measured with a skin electrode), and the function of the visual pathway with the flash and onset VEP protocols.

## 4 Conclusion

Clinical electrophysiological testing of the visual system allows an objective assessment of the visual system's function from the retinal pigment epithelium and up to the visual cortex. Testing can provide important information in the process of diagnosing certain eye diseases. Performing these methods is sensible only with specific clinical indications, and a broader clinical image should always be taken into account when evaluating results.

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## References

1. Robson AG, Nilsson J, Li S, Jalali S, Fulton AB, Tormene AP, et al. ISCEV guide to visual electrodiagnostic procedures. Doc Ophthalmol. 2018;136(1):1-26. DOI: 10.1007/s10633-017-9621-y PMID: 29397523
2. Constable PA, Bach M, Frishman LJ, Jeffrey BG, Robson AG; International Society for Clinical Electrophysiology of Vision. ISCEV Standard for clinical electro-oculography (2017 update). Doc Ophthalmol. 2017;134(1):1-9. DOI: 10.1007/s10633-017-9573-2 PMID: 28110380
3. McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, Tzekov R, et al. ISCEV Standard for full-field clinical electroretinography (2015 update). Doc Ophthalmol. 2015;130(1):1-12. DOI: 10.1007/s10633-014-9473-7 PMID: 25502644
4. Hood DC, Bach M, Brigell M, Keating D, Kondo M, Lyons JS, et al.; International Society For Clinical Electrophysiology of Vision. ISCEV standard for clinical multifocal electroretinography (mfERG) (2011 edition). Doc Ophthalmol. 2012;124(1):1-13. DOI: 10.1007/s10633-011-9296-8 PMID: 22038576
5. Bach M, Brigell MG, Hawlina M, Holder GE, Johnson MA, McCulloch DL, et al. ISCEV standard for clinical pattern electroretinography (PERG): 2012 update. Doc Ophthalmol. 2013;126(1):1-7. DOI: 10.1007/s10633-012-9353-y PMID: 23073702
6. Odom JV, Bach M, Brigell M, Holder GE, McCulloch DL, Mizota A, et al.; International Society for Clinical Electrophysiology of Vision. ISCEV standard for clinical visual evoked potentials: (2016 update). Doc Ophthalmol. 2016;133(1):1-9. DOI: 10.1007/s10633-016-9553-y PMID: 27443562
7. Hawlina M, Konec B. New noncorneal HK-loop electrode for clinical electroretinography. Doc Ophthalmol. 1992;81(2):253-9. DOI: 10.1007/BF00156014 PMID: 1468355
8. Jarc-Vidmar M, Popovič P, Hawlina M, Brecelj J. Elektrookulografija in slikovna elektroretinografija v diagnostiki Bestove viteliformne distrofije. Zdrav Vestn. 2002;71:II-109-18.
9. Brecelj J. Vidni evocirani potenciali in elektrofiziološko ocenjevanje vidne poti. Med Razgl. 1994;33(3):339-59.
10. Sustar M, Holder GE, Kremers J, Barnes CS, Lei B, Khan NW, et al. ISCEV extended protocol for the photopic On-Off ERG. Doc Ophthalmol. 2018;136(3):199-206. DOI: 10.1007/s10633-018-9645-y PMID: 29934802
11. Frishman L, Sustar M, Kremers J, McAnany JJ, Sarossy M, Tzekov R, et al. ISCEV extended protocol for the photopic negative response (PhNR) of the full-field electroretinogram. Doc Ophthalmol. 2018;136(3):207-11. DOI: 10.1007/s10633-018-9638-x PMID: 29855761
12. Thompson DA, Fujinami K, Perlman I, Hamilton R, Robson AG. ISCEV extended protocol for the dark-adapted red flash ERG. Doc Ophthalmol. 2018;136(3):191-7. DOI: 10.1007/s10633-018-9644-z PMID: 29934801
13. Sustar M, Hawlina M, Brecelj J. Electroretinographic evaluation of the retinal S-cone system. Doc Ophthalmol. 2011;123(3):199-210. DOI: 10.1007/s10633-011-9299-5 PMID: 22120511
14. Hood DC, Odel JG, Winn BJ. The multifocal visual evoked potential. J Neuroophthalmol. 2003;23(4):279-89. DOI: 10.1097/00041327-200312000-00010 PMID: 14663311
15. International Society for clinical Electrophysiology of Vision. Standards, Recommendations and Guidelines. Viusal Electrodiagnostics. A Guide to Procedures. Glasgow: ISCEV; 2019 [cited 2019 Dec 22]. Available from: http://www.iscev.org/standards/proceduresguide.html.

16. Lois N, Holder GE, Bunce C, Fitzke FW, Bird AC. Phenotypic subtypes of Stargardt macular dystrophy-fundus flavimaculatus. Arch Ophthalmol. 2001;119(3):359-69. DOI: 10.1001/archopht.119.3.359 PMID: 11231769
17. Glavač D, Jarc-Vidmar M, Vrabec K, Ravnik-Glavač M, Fakin A, Hawlina M. Clinical and genetic heterogeneity in Slovenian patients with BEST disease. Acta Ophthalmol. 2016;94(8):e786-94. DOI: 10.1111/aos.13202 PMID: 27775230
18. Boon CJ, Klevering BJ, Leroy BP, Hoyng CB, Keunen JE, den Hollander AI. The spectrum of ocular phenotypes caused by mutations in the BEST1 gene. Prog Retin Eye Res. 2009;28(3):187-205. DOI: 10.1016/j.preteyeres.2009.04.002 PMID: 19375515
19. Vincent A, Robson AG, Holder GE. Pathognomonic (diagnostic) ERGs. A review and update. Retina. 2013;33(1):5-12. DOI: 10.1097/IAE.0b013e31827e2306 PMID: 23263253
20. Sustar M, Perovšek D, Cima I, Stirn-Kranjc B, Hawlina M, Brecelj J. Electroretinography and optical coherence tomography reveal abnormal post-photoreceptoral activity and altered retinal lamination in patients with enhanced S-cone syndrome. Doc Ophthalmol. 2015;130(3):165-77. DOI: 10.1007/s10633-015-9487-9 PMID: 25663266
21. Sustar M, Stirn-Kranjc B, Brecelj J. Children with complete or incomplete congenital stationary night blindness: ophthalmological findings, standard ERGs and ON-OFF ERGs for differentiation between types = Otroci s prirojeno stacionarno nočno slepoto : oftalmološke značilnosti, standardni ERG ter ON-OFF ERG razlikovanje med kompletno in nekompletno obliko. Zdrav Vestn. 2012;81:16-28.
22. Gouras P, MacKay CJ, Lewis AL. The blue cone electroretinogram isolated in a sex-linked achromat. In: Drum B, Verriest G. Color Vision Deficiencies IX. Dordrecht: Kluwer; 1989. pp. 89-93. ;52. DOI: 10.1007/978-94-009-2695-0_8
23. Brecelj J. Visual electrophysiology in the clinical evaluation of optic neuritis, chiasmal tumours, achiasmia, and ocular albinism: an overview. Doc Ophthalmol. 2014;129(2):71-84. DOI: 10.1007/s10633-014-9448-8 PMID: 24962442
24. Jarc-Vidmar M, Tajnik M, Brecelj J, Fakin A, Sustar M, Naji M, et al. Clinical and electrophysiology findings in Slovene patients with Leber hereditary optic neuropathy. Doc Ophthalmol. 2015;130(3):179-87. DOI: 10.1007/s10633-015-9489-7 PMID: 25690485
25. Hawlina M, Strucl M, Stirn-Kranjc B, Finderle Z, Brecelj J. Pattern electroretinogram recorded by skin electrodes in early ocular hypertension and glaucoma. Doc Ophthalmol. 1989;73(2):183-91. DOI: 10.1007/BF00155036 PMID: 2638627
26. Cvenkel B, Sustar M, Perovšek D. Ganglion cell loss in early glaucoma, as assessed by photopic negative response, pattern electroretinogram, and spectral-domain optical coherence tomography. Doc Ophthalmol. 2017;135(1):17-28. DOI: 10.1007/s10633-017-9595-9 PMID: 28567618
27. Hawlina M, Šket-Kontestabile A, Brecelj J, Holder G.. Paraneoplastične retinopatije. Zdravn Vestn. 2005;74(10):643-7.
28. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF; American Academy of Ophthalmology. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). Ophthalmology. 2016;123(6):1386-94. DOI: 10.1016/j.ophtha.2016.01.058 PMID: 26992838
29. Fulton AB, Brecelj J, Lorenz B, Moskowitz A, Thompson D, Westall CA; ISCEV Committee for Pediatric Clinical Electrophysiology Guidelines. Pediatric clinical visual electrophysiology: a survey of actual practice. Doc Ophthalmol. 2006;113(3):193-204. DOI: 10.1007/s10633-006-9029-6 PMID: 17109158
30. Pompe MT, Liasis A, Hertle R. Visual electrodiagnostics and eye movement recording - World Society of Pediatric Ophthalmology and Strabismus (WSPOS) consensus statement. Indian J Ophthalmol. 2019;67(1):23-30. DOI: 10.4103/ijo.IJO_1103_18 PMID: 30574885
31. Brecelj J, Stirn-Kranjc B. Vidna elektrofiziologija pri otroku. Zdrav Vestn. 2005;74:631-41.
32. Brecelj J, Stirn-Kranjc B. Vloga elektrofiziologije vida v pediatrični oftalmologiji. Tečavčič Pompe M, Stirn Kranjc B, Cvenkel B, Globočnik Petrovič M, Vidović Valentinčič N. Otroška oftalmologija: izbrana poglavja iz oftalmologije. Ješetov dan. marec 2019; Ljubljana. Ljubljana: Univerzitetni klinični center, Očesna klinika; 2019.
33. Kurent A, Stirn-Kranjc B, Brecelj J. Electroretinographic characteristics in children with infantile nystagmus syndrome and early-onset retinal dystrophies. Eur J Ophthalmol. 2015;25(1):33-42. DOI: 10.5301/ejo.5000493 PMID: 25096283
34. Kurent A, Brecelj J, Stirn-Kranjc B. Electroretinograms in idiopathic infantile nystagmus, optic nerve hypoplasia and albinism. Eur J Ophthalmol. 2018;30(1):147-54. DOI: 10.1177/1120672118818322 PMID: 30541351
35. Brecelj J, Stirn-Kranjc B. Visual electrophysiological screening in diagnosing infants with congenital nystagmus. Clin Neurophysiol. 2004;115(2):461-70. DOI: 10.1016/j.clinph.2003.10.011 PMID: 14744589