UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
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PhD THESIS

ELECTRORETINOGRAPHIC CHANGES IN OPHTHALMOLOGIC PATHOLOGY

-ABSTRACT-

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Introduction

The integration of organisms into the environment is dependent on the perceived environmental informations, most of which is received through the visual analyzer. Thus, vision plays a major role in spatial orientation, maintaining balance in most of the specific human activities.

According to World Health Organization statistics, in 2014, 285 million people were reported to have visual problems, of which 39 million were blind and 246 million moderate-to-severe decrease in visual acuity. 82% of blind people are more than 50 years old, and 80% of them have a cause that can be treated or prevented.

Currently, there are a wealth of therapeutic means for people with blindness or visual dysfunction. Most frequently, emphasis is placed on morphological techniques, but which in the early stages do not change. Functional methods, such as electroretinograms, visual evoked potentials, or electrooculogram, although they can lead to a diagnosis prior to structural changes being installed, are rarely used, especially in our country. Based on these prerequisites, our research aims to bring to light the importance of electrophysiological explorations for an early diagnosis of vascular, degenerative and dystrophic ophthalmologic disorders, given the large number of people with visual disturbances and blindness that reside therefrom.

Key words: retina, electroretinogram, diabetic retinopathy, posterior vitreous detachment, cone dystrophy, cone-rod dystrophy.

Part I – Prior knowledge

Most of the information in the external environment is received through the visual analyzer. The eye is a very complex sensory receiver, consisting of several layers or tunics, which are the optic device and retina.

The retina is the innermost shell of the eye, located between the choroid and the vitreous. Although it contains millions of cells, it is a transparent and thin membrane of about 0.15 mm. [(1)]. Although the anatomy and histology of the retina are well known for over 100 years, the information generated by it and the way it is processed by various specialized cortical areas are still incompletely elucidated.

Each image, which the human eye sees, is transformed into an electrical signal. Electrophysiological tests record the electrical response of the retina, optic nerve or visual cortex. In this study, in order to evaluate retinal functional changes in vascular, dystrophic and degenerative ophthalmologic disorders, we considered electroretinography useful.

The electrical response of the retina to a luminous stimulus recorded on the cornea is the electroretinogram. Depending on the stimuli used, the recording conditions and the retinal cells that are being studied, the following types of electroretinogram were described: standard ERG, pattern ERG, multifocal ERG, photopic negativeg response, cone S ERG.

Among the components of the standard electroretinogram, waves "a", "b" and oscillatory potentials are real tools in evaluating retinal functionality.

Applications of standard electroretinography in ophthalmologic pathology

Diabetes mellitus (DM) is a major cause of disability, death, and economic loss all over the world, throught acute and chronic complications. [(2)] The most common retinal complication in DM is diabetic retinopathy (DR), which is considered to be a microangiopathy, which affects endothelial cells and pericytes. [(3)] More recent studies show that neurodegenerative processes are present before microcirculation changes are detected in ophthalmoscopic examination. [(4)] Thus, electrophysiological tests can be used to identify the degree of damage to retinal function in an objective manner. ERG is a test for assessing

retinal integrity in patients with diabetes with a sensitivity of the same or even greater than morphological investigations.

Posterior vitreous detachment (PVD) is defined as a separation between the posterior cortical vitreous hyaloid and the internal limiting membrane. [(5)] Most patients with PVD are asymptomatic and do not require treatment, [(6)] and symptomatic patients are being monitored closely. However, there are cases in which the posterior vitreous detachment generates complications in the retinal vitreous junction: epiretinal membrane, macular hole, vitreomacular traction syndrome, the point of departure being the vitreo-retinal residual adhesion.

In order to study the vitreoretin junction, both morphologically and functionally, the use of optical coherence tomography and electroretinography can provide important information in the diagnosis and monitoring of these patients.

Retinal dystrophies are chronic and progressive diseases that affect the visual function by altering photoreceptors in a variable proportion.

The standard electroretinogram represents the "gold technique" in the diagnosis of these diseases,[(7)] especially when the patients are asymptomatic or have a non-specific symptom, and the appearance of the fundus is normal.[(8)]

Part II –Personal contributions

1. Aim and objectives of the research

The main aim of the paper was to evaluate the changes in the standard electroretinogram in vascular, dystrophic and degenerative retinal and vitreoretin disorders, thus highlighting the role and importance of this investigation in the diagnosis and monitoring of various ophthalmologic diseases.

To achieve the main purpose of our study, we have formulated the following specific objectives:

- Establishing a working reference for the equipment used.
- Investigation of standard electroretinogram in patients with type 2 diabetes at various stages of retinal involvement.
- electroretinogram evaluation in patients with vitreous posterior detachment and various complications resulting from this condition, in parallel with the morphological examination by means of optical coherence tomography.
- recording electroretinogram in patients with cone dystrophy and cone-rod dystrophy, at two moments of disease progression, in parallel with morphological examination by optical coherence tomography.

2.Lots and methods

2.1. Lots

The objectives described above were performed in two laboratories using different equipments and lots of distinct subjects. Each objective was accomplished as follows:

- the REF (reference) study included a batch of 54 healthy subjects aged 20 to 80 years;
- the DM trial was performed in a batch of 44 patients with type 2 diabetes, grouped in four sublots depending on diabetic retinopathy severity and compared with 14 healthy subjects ;
- the PVD study was conducted in a group of 10 subjects with vitreous posterior detachment and various complications of this disorder;
- The CD / CRD study comprised a group of 8 patients with cone dystrophy and cone-rod dystrophy.

The REF, DM and PVD studies were conducted within the Diabetic Eye Compartment of SCJU Craiova and the Ocularius Ophthalmology Research Center, and the CD / CRD study

was realized in the Department of Electrophysiology of the University Eye Hospital, Ljubljana, Slovenia .

We conducted these experiments taking into account the ethical and deontological principles of the Helsinki Declaration of Human Rights. Each subject was informed of the purpose of the experiment and how it was deployed and expressed its consent to voluntary participation, under the circumstances.

2.2 Equipments and methods

Each subject participating in the study was performed the following protocol:

1. Ophthalmic examination: measurement of visual acuity; Intraocular pressure measurement; Biomicroscopic examination of the anterior pole; refractokeratometry; Ishihara test; Biomicroscopic examination of the retina

2. Recording the electroretinogram

We used Metrovision MonPackOne (Metrovison, Perenchies, France) to perform REF, DM and PVD studies and Espion Diagnosys for the CD / CRD study, according to the protocol of the International Society of Electrophysiology of Vision.[9]

3. Top-eye photography using the TopCon TRC-NW6S system for DM study and Heidelberg Spectralis HRA + OCT in the CD / CRD study

4. Performing optical coherence tomography using the TopCon 3D OCT-2000 and Optovue Ivue systems for the DPV study and the Heidelberg Spectralis HRA + OCT system for the DC / DCB study**.**

2.3 Statistical analysis of the data

The statistical processing of the data obtained from this research was done with the Microsoft Excel program (Microsoft Corp., Redmond, WA, USA), together with the XLSTAT suite for MS Excel (Addinsoft SARL, Paris, France) and the Vision Monitor integrated software The Metrovision MonPackOne system. [10]

Secondary data processing, calculation of fundamental statistical parameters, mean and standard deviation, their ratio - coefficient of variation, data comparison was performed using Excel, through ANOVA, post-hoc Fisher LSD and non-parametric Wilcoxon test

The graphical representation of the data was accomplished with Microsoft Excel through the Pivot Tables, Functions-Statistical, Chart and Data Analysis modules, and the CD / CRD study used the MedCalc software.

3. Results and discussions

3.1 Results and discussions following testing of the control batch

In the REF study, we recorded 54 standard electroretinograms, according to the International Society of Electrophysiology of Vision protocol, in 54 healthy subjects, 30 men and 24 women. Since there were no significant differences between the two eyes, we used the mean between the right eye and the left eye for each subject. Also, there were no statistically significant differences between women and men, so statistical data was processed in the five age categories, not gender-specific.

For each age group, we analyzed the latency of the following waves: "a" and "b" in Scotopic 0.01, Scotopic 3.0, PPhotopic 3.0, Photopic 30 Hz Flicker, and P1, P2 in Scotopic 3.0 oscillatory potential;

By analyzing the "a" wave latency variation in Scotopic 0.01, a significant difference was observed between subjects aged 19-29 years, 30-39 years and subjects over 40 years.

Regarding the variation of "b" wave latency in Scotopic 0.01, a significant difference was observed between all age groups except for the 19-29 age groups versus 30-39 years and 50-59 years versus the subjects over 60 years.

Analyzing the latency of the "a" wave in the evaluation of mixed rod-cone responses by Scotopic 3.0 record, we obtained a significant difference between the subjects under 40-year-old (19-29 years, 30-39 years) versus the 40-49, 50- 59 years and subjects over 60 years old.

The "b" wave latency variation in Scotopic 3.0 ERG shows a statistically significant difference between all age groups, with the exception of subjects in the 19-29 age groups and 40-49 years.

The oscillatory potentials latency variation in Scotopic 3.0 OPs record, show no statistically significant difference for the P1 and P2 waves in any of the five age groups.

By analyzing the latency variation of "a" wave in Photopic 3.0, we did not get any significant difference between the five age groups. Wave "b" latency in the Photopic 3.0 record showed a significant difference between subjects in the 19-29 age group and all subjects in the two groups over 50 years.

Analyzing the variation of "a" wave latency in Photopic 30 Hz Flicker record, we did not get any significant difference between the five age groups. From the wavelength variation chart of "b" wave latency in Fotopic 30 Hz Flicker, we obtained differences between subjects in the 19-29 age group and subjects in groups 50-59 and over 60 years.

By analyzing "a" and "b" wave latency in subjects aged 19 to 80, grouped into five age groups: 19-29 years, 30-39 years, 40-49 years, 50 -59 years,> 60 years old, we obtained statistically significant differences, both in scotopic and photopic conditions. (11)

In our study, latency changes were higher in the scotopic system compared to photopic system. Thus, in subjects over 50 years of age in scotopic records, both "a" and "b" wave have a statistically significant increase in latency, but only "b"wave is characterized by its increase in the group of subjects over 60 years old. (11)

Regarding oscillatory potentials, none of the four peaks had a statistically significant increase in latency in the five age groups. (11)

Thus, our results show earlier injury to rod cells compared to cone cells.

3.2 Results and discussions following testing of diabetic subjects

In this study we evaluated ophthalmologically and electroretinographically 44 subjects diagnosed with type 2 diabetes mellitus and various stages of diabetic retinopathy, which we compared with 14 healthy subjects.

Regarding the standard electroretinogram latencies, we noticed differences between the left eye and the right eye, we analyzed each eye, the study including 88 diabetic eyes and 28 healthy eyes.

After comparing wavelength latency "a" in the Scotopic 0.01 record, we found statistically significant differences ($p = 0.0333$) in the five sublots using the ANOVA test. In order to spot the group pairs between which these differences were manifested, we went to the post-hoc Fisher LSD test. Thus, major changes of the "a" wave were between healthy subjects and those with non-proliferative and proliferative diabetic retinopathy

Concerning the "b" wave latency in Scotopic 0.01 record, we obtained a significantly high overall difference among subjects in the five groups. The main subgroups between which this difference was manifested were subjects with laser treated proliferative diabetic retinopathy and proliferative diabetic retinopathy versus subjects included in the first three sublots.

By analyzing the "a" wave latency in the Scotopic 3.0 record, neither the Anova test nor the post-hoc Fisher LSD test showed statistically significant values.

Following the evaluation of the "b" wave latency in the Scotopic 3.0 record, we identified a significant overall difference ($p = 0.006$).

With the Fisher LSD post-hoc test, we noticed that this difference is due, in particular, to the latency changes occurring between the subjects in the PDR-laser treated sublot and the subjects in the control and NDR sublots.

Oscillatory potentials are characterized by a high, overall significant increase in latency for both P1 and P2, with "p" ANOVA values of 0.000.

By analyzing the five sublots, using the Fisher LSD post-hoc test, we noticed that for P1 wave, significant differences arose between the sublot with proliferative diabetic retinopathy and subjects in the control, diabetes without diabetic retinopathy and non-proliferative diabetic retinopathy sublots, and between the sublot with laser treated proliferative diabetic retinopathy and the control and diabetic without retinopathy subgroups. Concerning P2 wave, the pot-hoc Fisher LSD test showed major changes between the control sublot and all four other groups.

Analyzing the "a" wave latency in the Fotopic 3.0 record, we noticed a significant overall difference due to significant increases in latency between subjects with proliferative diabetic retinopathy and laser treated proliferative diabetic retinopathy versus healthy subjects and those with diabetes but without diabetic retinopathy . Concerning the "b" wave of the Fotopic 3.0 record, we have seen a significant collective difference. This is due to the major increase in latency in the sublot of subjects with proliferative diabetic retinopathy compared to all the other four groups included in the study.

The response of the cone cells, assessed using the photopic 30 Hz flicker record of the standard electroretinogram, was characterized by a significant change in latency for both "a" ($p = 0.006$) and "b" wave ($p = 0.002$)). For both waves, the Fisher LSD post-hoc test showed that this overall difference was due to increased latency in the sublot of laser treated proliferative diabetic retinopathy compared to all other groups for "a" wave, and for "b" wave with the sublot Control, DM sublot and PDR sublot.

Our study, although not including a very large number of subjects, has followed and compared functional aspects in several stages of diabetic retinopathy severity.

All parameters analyzed in this study showed a statistically significant change, except for the "a" wave in Scotopic 3.0 record , which evaluates the mixed cone-rod response.

The first identified electroretinographic change is the increase in latency of the second wave of oscillatory potentials in subjects diagnosed with type 2 diabetes mellitus without diabetic retinopathy compared to the control sublot. [(12)]

In our study, between healthy subjects and those with diabetes without diabetic retinopathy, we did not achieve any statistically significant change than that reported in oscillatory potentials. This is probably due to the exclusion of age differences.

With the evolution of ocular damage, in our tests, we have achieved a significant increase in the latency of the "a" wave in scotopic recording. Thus, in subjects with non-proliferative diabetic retinopathy, we noticed a increase in the "a" wave latency of the rod cell response.

Regarding the sublot of subjects with proliferative diabetic retinopathy, the main increases in latency were: the "b" wave in rod response and cone-rod response and the "a" wave of cone cells.

Evaluation of subjects in the sublot with proliferative diabetic retinopathy and laser treatment showed a predominant involvement of the photopic system, namely flicker stimulation.

3.3. Results and discussions following testing of posterior vitreous detachment subjects

Of the 100 patients suspected of posterior vitreous detachment and its complications that presented in the our Clinic between June 2014 and January 2015, nine of them met the inclusion / exclusion criteria of our study.

Thus, we present nine non-consecutive cases, with pathology of the vitreo-retinal junction, with obvious or less pronounced changes in the clinical ophthalmologic examination, but very well revealed through optical coherence tomography. The appearance of the standard electroretinogram is variable, depending on the degree of retinal damage.

The 9 patients enrolled in our study were diagnosed with posterior vitreous detachment and various complications as follows: four with epiretinal membrane with vitreoretinal tractional syndrome, one with intraretinal cystic spaces, two with lamellar macular hole, four with full-thickness macular hole, and one of the subjects with “bursa premacularis”.

In case of ”bursa premacularis” presence, we noticed a normal aspect of the fundus, but the optical coherence tomography shows the detachment of the posterior hyaloid in the temporal and nasal quadrants, but which remains attached to the foveolar region, as well as an "empty space " in the premacular area, suggesting stage 2 PVD and ”bursa premacularis”. The standard electroretinogram shows a normal retinal function. (13)

Regarding the epimacular membrane, it was identified in four of the nine subjects included in the batch. Optical coherence tomography is the most commonly used method for diagnosing this structure, as well as highlighting its effects on the retina: increased retinal thickness, traction, macular edema, damage of the normal retinal architecture. The standard electroretinogram was normal in two of the four subjects, and in the other two, the cone cell response was diminished, but they also had other complications, such as macular hole.

This fact suggests that the epiretinal membrane does not sufficiently influence retinal function to affect the standard electroretinogram, as it is known that the standard ERG is affected when more than 20% of the retinal cells are damaged.

Of the nine subjects enrolled in the study, one has an intraretinal pseudochist, two lamellar macular holes and four complete macular holes. Optical coherence tomography has a major role in detecting, monitoring, and establishing the surgical indication of macular holes.

Regarding the standard electroretinogram, it was only affected in subjects who had a full-thickness macular hole and normal in those who were diagnosed with lamellar macular hole or intraretinal pseudochist.

Modification of the standard electroretinogram consisted in affecting the response of cone cells with normal rod cell response. (13)

3.4. 3.4. Results and discussions following testing of subjects with retinal dystrophies

The CD / CRD study included 8 subjects diagnosed with cone dystrophy and cone-rod dystrophy, which were evaluated ophthalmologically and electroretinographically at least twice, in order to dynamically monitor the morphological and functional changes occurring in these diseases.

The results of the ophthalmologic examination were variable. The appearance of the fundus ranged from normal to the characteristic appearance of "bull-eye" maculopathy. Seven of the eight patients included in the study were myopic, but none showed nystagmus.

In terms of chromatic vision testing by the Ishihara test, it was affected in all subjects, except for a patient with cone-rod dystophy.

The results of the optical coherence tomography were variable, from the normal aspect to the atrophy of the photoreceptor layer.

To perform this study, we analyzed the electroretinograms of 8 patients, performed in two examinations, at 6.3 years for cone dystrophy and 5.4 years for cone-rod dystrophy, along with the morphological information obtained fromretinal photography and optical coherence tomography of the macular region

Because in many cases there was a significant difference between the electroretinographic parameters recorded in the right eye and the left eye, we analyzed each eye individually. Thus, for each of the 16 eyes we calculated the latency and amplitude for : "b" wave in Scotopic 0.01 and Photopic 30 Hz Flicker and "a" and "b" waves in Scotopic 3.0 and Photopic 3..

By analyzing the amplitude of "a" wave in Scotopic 3.0 record, in patients with cone dystrophy and cone-rod dystrophy, we did not obtain a statistically significant difference in its variation between the two examinations.

The variation in ”a” wavelength latency between the two examinations, in the evaluation of the mixed cone-rod response, did not show a statistically significant difference either in the cone dystrophy subjects or in the cone-rod dystrophy .

Regarding the mean amplitude and mean latency of the "b" wave in the Scotopic 3.0 record, neither the cone dystrophy nor the cone-rod dystrophy subjects showed a statistically significant evolution between the two examinations.

Analyzing the variation in mean amplitude and latency of "b" wave, in order to evaluate the change of rod cells response between the two investigation periods, we did not obtain a statistically significant difference in any of the batches, although in the case of the cone-rod dystrophy the mean amplitude is low compared to laboratory standards.

Following the assessment of the "a" wave in the Fotopic 3.0 record, only the mean amplitude in the cone dystrophy subjects changed statistically significantly between the two examinations, while in the case of the patients with the cone-rod dystrophy , this parameter remained constant. Also, the mean latency does not show a statistically significant evolution, although its value is below laboratory limits, at both investigative periods.

By analyzing the mean amplitude of "b" wave in Fotopic 3.0, although below normal for both cone dystrophy and cone-rod dystrophy, the variation is not statistically significant between the two explorations.

Regarding average latency, it remains constant between the two examinations in both groups.

From the amplitude plot of the "b" wave amplitude of the 30 Hz Flicker record, which evaluates the cone response, both for the cone dystrophy and thecone-rod dystrophy subjects, we achieved a statistically significant evolution between the first and the second examination.

The average latency was higher than the normal value of the laboratory in all cases, but we achieved a statistically significant evolution only in the case of subjects with cone-rod dystrophy between the two exploration periods.

In the case of the cone dystrophy subjects, we obtained changes only for photopic records, the scotopic ones being within normal limits.

By comparing the mean values between the two examinations, we obtained statistically significant differences for the mean amplitude of the "a" wave in the Photopic 3.0 record and for the mean amplitude of "b" wave in the Flicker 30 Hz record. The average amplitude of all waves in scotopic records was within normal range.

Also, for the average latency of all the waves, both in the photopic and scotopic systems, we did not obtain statistically significant differences between the two examinations

All subjects with cone-rod dystrophy showed a low amplitude of all waves, both in photopic conditions and in scotopic conditions.

Regarding the evolution of the photoreceptors function, the comparison of mean amplitude and ERG latency values showed a statistically significant difference in Photopic 30 Hz Flicker recording, with decrease of amplitude and increase of latency. Although low, rod cell response remained stable between the two examinations.

4.Conclusions

- Standard electroretinography represents the electrical response of the retina to a luminous stimulus and provides important information about the integrity of retinal neuron function in various ophthalmic and neuro-ophthalmic disorders.
- Age is one of the factors that can influence the components of the standard electroretinogram, affecting ,especially, the function of the photoreceptors.

- Rod cells are more functionally affected by age than cone cells, with a marked decrease in response to subjects over 50 years of age.
- Cone cells are characterized by a moderate impairment of their function in subjects over 60 years of age
- Neuronal synaptic activity between amacrine and retinal horizontal cells is unaffected by age, with oscillatory potentials remaining stable.
- The sex of the subjects did not influence the parameters of the ERG waves.
- Electroretinography is a useful technique in assessing retinal function in all stages of diabetic retinopathy.
- Subjects with type 2 diabetes, but without changes in diabetic retinopathy, show an increase in latency of the oscillatory potentials, which demonstrates an early alteration of neuronal activity of retinal amacrine and horizontal cells.
- With the installation of lesions specific to non-proliferative diabetic retinopathy, there is an alteration of rod cell function, electroretinographically translated, by increasing of "a" wave latency in scotopic records. The photopic system is not affected in the early stages of diabetic retinopathy.
- After the appearance of the neoformation vessels, we noticed a marked alteration of the scotopic system, with damage to the retinal inner layers (increase of wavelength "b"), but also the photoreceptors in the photopic system (the increase of the wavelength of "a").
- Subjects with proliferative diabetic retinopathy who have undergone laser treatment have an altered response to flicker stimulation. This response translates into damage to neurovascular coupling, i.e. the reduction in vasodilator capacity of retinal microcirculation, secondary to both destruction of retinal neurons and microcirculation.
- ”Bursa premacularis”, a vulnerability point in the premacular cortical vitreous, was identified by means of optical coherence tomography, which is a morphological investigation, with a normal electroretinographic response.
- The epiretinal membrane is a structure whose appearance is closely related to the posterior vitreous detachment, being well-documented by the optical coherence tomography, without affecting the functionality of the retina.
- The macular hole is a complication resulting from posterior vitreous detachment. Optical coherence tomography is the investigation that has a major role in detecting this pathology, and the electroretinogram is characterized by diminishing the photopic response in the case of the complete macular hole, without any alterations in the lamellar macular hole or intraretinal pseudochist.
- In cone dystrophy, we noticed a significant reduction in the photopic response without affecting the rod cell function. Evolutionally, the affection was characterized by the diminution of the waves in the photopic recordings, with normal scotopic response.
- In cone-rod dystrophy, both the function of the cone cells and of the rod cells was impaired. Progression of the disease was characterized by marked alteration of the cone cell system. The rod cell response, though low, remained stable between the two examinations.

The value of our study is validated by performing both functional and morphological tests in ophthalmic disorders, highlighting the contribution of electrophysiological examinations in the early detection of pathological, sometimes even "subclinical" aspects, thus offering the possibility of introducing treatments even in the initial stages of the disease, improving evolution and prognosis of diseases in this field.

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