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Full-field electroretinogram in evaluation of the outer retina in patients with multiple sclerosis

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Abstract---Background: Background: Optic nerve inflammation may contribute to the pathology of multiple sclerosis (MS) (retrograde trans-synaptic degeneration) However, within the past ten years, some investigations have indicated that primary retinopathy may be brought on by MS. This study used a full-field electroretinogram to test the function of the outer retinal layers in people with relapsing remitting multiple sclerosis (RRMS) (ff-ERG). Methods: This is a case-control study, conducted on 30 RRMS patients and 30 healthy controls. RRMS patients were subjected to neurological, ophthalmological, and radiological assessment. Both RRMS patients and controls were subjected to full field ERG. Results: The ff-ERG showed a significant delay of latencies of a and b-waves of both light and dark-adapted condition with reduction of their amplitudes compared to control. ERG responses were significantly affected in MS patients with or without optic neuritis compared to control. Most of ff-ERG parameters showed non statistically significant difference

between optic neuritis and non-optic neuritis eyes. Conclusion: There is functional affection of the bipolar and the photoreceptors layers in the outer retina in optic neuritis and non-optic neuritis eyes of MS. Therefore, the outer retina could be a site for primary pathology in MS, unrelated to the optic nerve affection.

Keywords---Multiple Sclerosis, Full-field ERG, Outer retina.

Background

The most prevalent immune-mediated inflammatory demyelinating disease of the central nervous system is multiple sclerosis (MS), which mostly affects the white and gray matter of the brain and spinal cord [1]. The retina and primary visual cortex are just two examples of the visual pathway that might be impacted by MS. Optic neuritis is thought to have affected 40% of MS patients as their initial clinical demyelinating event and up to 80% of them at some point during their illness [2]. According to research, MS-related retinal atrophy results from optic nerve inflammation and mostly affects the Inner Nuclear Layer, which is formed by ganglion cells [3,4]. But over the past ten years, some investigations have indicated that MS may result in primary retinopathy, which is a sign of atrophy in the central nervous system.[5]

Few studies have recently looked at the outer retina, which is separate from the ganglion cells that are affected by the optic nerve inflammation in MS, functionally and structurally by ERG. They discovered retinal abnormalities in the outer retinal layer, not related to the retrograde degeneration that occurs after optic neuritis, [6 -7]. In the full-field ERG (ff-ERG), which evaluates retinal function globally, the a-wave is produced by the photoreceptors and the b-wave by the bipolar cell [8]. Electroretinography (ERG) is used to evaluate the function of the retina.

As a result, retinal ganglion cells are believed to contribute little to nothing to ff-ERG waveforms. They can therefore be utilized to evaluate the outer retina without taking into account the effects of optic nerve inflammation.[9] The objective of this study was to use full-field ERG to functionally evaluate the outer retinal layers in patients with relapsing remitting multiple sclerosis when they were in remission.

Methods

This is a case-control study was conducted in the Neurodiagnostic and Research Center (NDRC), clinical neurophysiology department , Beni-Suef University Hospital, Beni-Suef ,Egypt during the period from February 2019 to February 2021.

Ethical Considerations: Ethical approval was obtained from the Research Ethical committee, Faculty of medicine, Beni-Suef University . Written informed consents were taken from the participants. The study was done in accordance with the principles of the Declaration of Helsinki.

Eligability Criteria: This study includes 30 patients (during remissions) diagnosed with relapsing remitting multiple sclerosis (RRMS) according to the International Panel on Diagnosis of Multiple Sclerosis “McDonald’s criteria 2017 [10].

We excluded Patients with a history of any associated autoimmune diseases, malignancy, diabetes mellitus, or hypertension. Patients with diagnosis of degenerative or inflammatory diseases of the retina, achromatopsia, or cone-rod dystrophies. Patients with a history of any neurological diseases other than MS is known to affect vision. Patients with a history of drugs intake known to affect the retina. Patients with a history of exposure to toxic substances, alcohol, heavy metals, or any substance known to affect the retina. Pregnant patients

Methods

Neurological assessment: All patients were subjected to: Thorough history taking regarding disease duration, total number of relapses, history of optic neuritis and Expanded Disability Status Scale (EDSS). Magnetic resonance imaging (MRI) on the brain, cervical and dorsal segments of spinal cord was performed for all included patients.

Ophthalmological assessment: Both patient and control were subjected to Visual acuity, Errors of refraction, Pupil examination, Fundus examination and Color vision.

Neurophysiological assessment: Full-field ERG testing was done to patients and control according to the international standards developed by the ISCEV in 2014 [11]. The device which was used for the tests is RETiport/scan 21 visual electrophysiological system of ROLAND CONSULT.

Binocular full field ERGs were recorded simultaneously. The pupils were dilated with topical 0.5% tropicamide and 0.5% phenylephrine hydrochloride. (Pupil diameter $\geq$ 8mm). Local anesthetics on the cornea were performed after dark adaptation for 20 min. The H-k loop electrodes were installed under the dim red light. Two Skin reference electrodes were installed on the orbital rim, around the outside of the eyes (right eye-side electrode connected to amplifier. Skin ground electrode was installed on the forehead and must be far from the reference electrodes. The skin electrodes were placed using a skin cleaning cream (new prep).

The body position of patients was comfortable; the head was fixed before the stimulator starts and the eye was fixated to the red light point in the Ganzfeld globe. The tests were started 20 minutes after dark adaptation. Impedance was tested to be less than 5kOhm. Scotopic 0.01 ERG, Scotopic 3.0 ERG, Scotopic 3.0 oscillatory potentials, (auto light adaptation 10 minutes), Photopic 3.0 ERG, Photopic 3.0 flicker were selected successively.

Statistical analysis: For statistical analysis SPSS version 25 (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) was used. Descriptive analysis of the results in the form of percentage distribution for qualitative data and (mean and standard deviation) calculation for quantitative data. Cross

tabulation and Chi Square test (χ^2) was employed to compare categorical variables and percentage values, exact test was used instead when the expected frequency is less than five. Independent sample t-test was used For comparison between means of two unrelated groups with a normal distribution. One-way analysis of variance (ANOVA) test was used to elucidate significance among group means, followed by Tukey's post-hoc test to compare mean values pair-wise. Differences were considered significant at p-values ≤ 0.05 . Total p. value for ANOVA was calculated and written, p-values of post hoc analysis were expressed as small letters ^(a,b,c). P-values equal to or less than 0.05 were considered statistically significant.

Results

The study included 41 (69.3%) females and 19 (31.7%) males without a statistically significant difference between cases and controls, (p-value < 0.05). The mean value for age was 34.77 ± 8.34 years without a statistically significant difference between cases and controls, (p-value > 0.05). The mean disease duration was 78.57 ± 66.76 months. The mean value for Expanded disability scale (EDSS) among studied MS patients was (3.033 ± 1.53) points. The mean value for MRI lesion load was (10.53 ± 4.66) points. History of optic neuritis (ON) were obtained for a total of 60 eyes (from 30 MS patients). Regarding history of ON, 23 (38.3%) of the studied MS eyes have a history of ON. Full field Electroretinography (ff-ERG) responses from patients with MS were compared with those from the control group, and descriptive data is provided in Table 1.

The dark adapted 0.01 rod response b wave showed significantly delayed latency in MS patients as compared with healthy controls, while for the amplitude (μV) there was non-statistically significant difference between MS and healthy eyes. The dark adapted 3.0 combined rod and cone response, (a and b) waves showed significantly delayed latency in MS patients as compared with healthy controls. At the same time, amplitudes for (a and b) waves were significantly lower in the MS patients as compared with healthy controls. However, in the b-wave / a-wave ratio, there was non-statistically significant difference between MS and healthy eyes. Dark-adapted 3.0 oscillatory potentials showed significantly delayed latency in MS patients as compared with healthy controls. The light adapted 3.0 cone response (a and b) waves showed significantly delayed latency in MS patients as compared with healthy controls. At the same time, amplitudes for a, and b waves were significantly lower in the MS patients as compared with healthy controls. Light-adapted 3.0 flicker (30 Hz flicker) showed significantly delayed latency in MS patients as compared with healthy controls. While amplitude was significantly lower in the MS patients as compared with healthy controls.

Table 1: Full field electroretinography responses in the included MS patients compared to healthy controls

		Studied Eyes		<i>p-value</i>
		Healthy Eyes N= 60	MS Eyes N= 60	
1) Dark-adapted 0.01 ERG (rod response)				
0.01 Latency b wave	Mean ±SD	76.10 ±5.32	87.28 ±7.78	0.001*

0.01 amplitude b wave	Mean $\pm$ SD	140.93 $\pm$ 59.12	119.85 $\pm$ 61.81	0.051
(2) Dark-adapted 3.0 ERG (combined rod-cone response)				
3.0 Latency a wave	Mean $\pm$ SD	19.30 $\pm$ 2.93	21.30 $\pm$ 3.23	<0.001*
3.0 amplitude a wave	Mean $\pm$ SD	122.49 $\pm$ 35.34	98.18 $\pm$ 35.00	<0.001*
3.0 Latency b wave	Mean $\pm$ SD	39.15 $\pm$ 4.01	47.40 $\pm$ 7.97	0.001*
3.0 amplitude b wave	Mean $\pm$ SD	228.12 $\pm$ 70.36	191.03 $\pm$ 76.20	0.007*
b/a ratio	Mean $\pm$ SD	1.93 $\pm$ 0.34	2.05 $\pm$ 0.56	0.143
(4) Dark-adapted 3.0 oscillatory potentials				
op p2 Latency	Mean $\pm$ SD	25.57 $\pm$ 1.25	26.57 $\pm$ 1.61	<0.001*
(5) Light adapted 3.0 ERG (cone response)				
3.0 Latency a wave	Mean $\pm$ SD	14.94 $\pm$ 1.20	16.41 $\pm$ 1.53	0.001*
3.0 amplitude a wave	Mean $\pm$ SD	25.55 $\pm$ 9.54	20.28 $\pm$ 6.95	0.001*
3.0 Latency b wave	Mean $\pm$ SD	30.95 $\pm$ 1.20	32.23 $\pm$ 1.36	0.001*
3.0 amplitude a wave	Mean $\pm$ SD	98.92 $\pm$ 32.83	76.48 $\pm$ 25.69	0.001*
(6) Light-adapted 3.0 flicker (30 Hz flicker)				
P1 latency	Mean $\pm$ SD	62.32 $\pm$ 1.76	63.85 $\pm$ 2.62	0.001*

*p-value ≤ 0.05 is considered statistically significant, Statistical analysis was carried out using independent sample t-test.

The comparison of the ff-ERG responses from the MS patients in relation to optic neuritis as compared to healthy controls provided in Table 2. The dark adapted 0.01 rod response, b wave latency showed non-statistically significant difference between MS-ON patients as compared with MS-non-ON patients, while both groups showed significantly delayed b wave latency as compared with healthy controls. Dark-adapted 3.0 ERG (combined rod-cone response), b wave amplitude was significantly lowest in the MS-ON patients as compared with both MS-non-ON patients and healthy controls, while there was non-statistically significant difference between MS-non-ON patients and healthy controls. Dark-adapted 3.0 oscillatory potentials showed non-statistically significant difference between MS-ON patients as compared with MS-non-ON. The comparison of the ff-ERG responses from the MS patients in relation to optic neuritis as compared to healthy controls showed non-statistically significant differences in all light adapted ff-ERG between MS-ON patients as compared with MS-non-ON.

Table 2: Full field Electroretinography responses in MS patients with and without optic neuritis compared to healthy controls

		Studied Eyes			<i>p-value</i>
		Healthy Eyes N= 60	MS non-ON Eyes N= 23	MS ON Eyes N= 37	
(1) Dark-adapted 0.01 ERG (rod response)					
0.01 Latency b wave	Mean ±SD	76.10 ±5.32	87.23 ±8.22	87.35 ±7.20	<0.001* <0.001* 0.947
0.01 amplitude b wave	Mean ±SD	140.93 ±59.12	127.63 ±55.82	107.33 ±69.86	0.025* 0.294 0.207

(2) Dark-adapted 3.0 ERG (combined rod-cone response)					
3.0 Latency a wave	Mean ±SD	19.30 ±2.93	21.21 ±3.57	21.44 ±2.66	0.006* 0.004* 0.777
3.0 amplitude a wave	Mean ±SD	122.49 ±35.34	103.23 ±36.18	90.07 ±32.14	<0.001* 0.010* 0.160
3.0 Latency b wave	Mean ±SD	39.15 ±4.01	48.27 ±9.30	45.99 ±5.03	<0.001* <0.001* 0.175
3.0 amplitude b wave	Mean ±SD	228.12 ±70.36	207.32 ±75.49	164.83 ±71.31	<0.001* 0.171 0.028*
b/a ratio	Mean ±SD	1.93 ±0.34	2.13 ±0.66	1.92 ±0.31	0.032* 0.935 0.077
(3) Dark-adapted 3.0 oscillatory potentials					
op p2 Latency	Mean ±SD	25.57 ±1.25	26.41 ±1.62	26.81 ±1.60	0.006* 0.001* 0.304
4) Light adapted 3.0 ERG (cone response)					
3.0 Latency a wave	Mean ±SD	14.94 ±1.20	16.24 ±1.63	16.69 ±1.35	<0.001* <0.001* 0.213
3.0 Latency b wave	Mean ±SD	30.95 ±1.20	32.00 ±1.29	32.60 ±1.41	<0.001* <0.001* 0.078
3.0 amplitude a wave	Mean ±SD	25.55 ±9.54	20.72 ±7.33	19.58 ±6.37	0.007* 0.004* 0.609
3.0 amplitude a wave	Mean ±SD	98.92 ±32.83	80.20 ±26.97	70.49 ±22.78	0.003* <0.001* 0.216
(5) Light-adapted 3.0 flicker (30 Hz flicker)					
P1 latency	Mean ±SD	62.32 ±1.76	64.10 ±2.78	63.44 ±2.33	<0.001* 0.042* 0.271
N1-P1 Amplitude	Mean ±SD	69.86 ±16.94	57.02 ±17.32	55.19 ±17.59	<0.001* <0.001* 0.689

MS: Multiple Sclerosis, ON: Optic Neuritis

*p-value ≤0.05 is considered statistically significant

Statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by Tukey's post hoc analysis.

- ^a P-value for MS ON vs. Control.
- ^b P-value for MS non-ON vs. Control
- ^c P-value for MS ON vs. MS non-ON.

Discussion

The outer retinal preganglionic elements as photoreceptors and bipolar cells are located away from the ganglion cells of the inner nuclear retinal layer which may be affected by optic nerve inflammation in MS. Thus, it is of great interest to assess the outer retina and to figure out whether outer retinal preganglionic elements are involved in the neurodegenerative process of MS in the occurrence of optic neuritis or not [6,7]. The aim of our study was to do functional assessment of the outer retinal layers in patients with relapsing remittent multiple sclerosis during remission by full-field.

Electroretinography (ERG) is used for functional evaluation of the retina. The full-field ERG (ff-ERG) assesses the global retinal function and generated by the photoreceptors and the bipolar cell layer [8]. Full-field-ERG waveforms are thought to receive little or no contribution from the retinal ganglion cells. This means that they can be used to assess the outer retina independently from optic nerve inflammation [9].

Affection of a and b waves signify dysfunction of both rod and cone photoreceptors as well as bipolar cells of the whole retina. The a-wave was presumed to be generated by the photoreceptors, and the b-wave generated by the bipolar cell layer [8]. Our results revealed signs of dysfunction of both rod and cone photoreceptors as well as bipolar cells of the whole retina in eyes with and without optic neuritis. These were demonstrated in prolonged latencies and reduced amplitudes of the a and b waves of the dark-adapted (combined rod-cone responses and oscillatory potentials) and the light-adapted (cone and flicker) responses in MS patients compared to controls. However, only a significant delay in the latency of b-wave of the dark-adapted rod response without difference in amplitudes was reported. There was also no significant difference in the b-wave /a-wave amplitude ratio between patients and controls. Almost all our results showed no significant differences between MS optic neuritis - eyes as compared with MS- non-optic neuritis eyes except for the amplitude of b-wave of combined rod and cone response which showed significant differences in MS optic neuritis.

A plenty of studies demonstrated delayed latencies of the cone or combined rod/cone ERG responses [12, 13, 7], while others showed delayed latencies of the rod response [14]. However, the analysis of the amplitudes showed contradictory results, some showed normal amplitudes [13,7] while others showed reduced amplitudes[5] in MS patients relative to control groups. These could be attributed to the different phenotypes of MS patients, presence or absence of optic neuritis, acquisition systems, and analysis of recordings and reduced databases [7].

In 2018, Hanson et al, found a significant difference in the latencies of a and b waves of the cone and combined rod/cone responses, between MS patients and controls [7]. However, our data differ regarding amplitudes which were mostly normal in their study. This may be explained by the longer disease duration and higher EDSS in our patients. This explanation is supported by the longitudinal study carried out by You et al., 2017 on MS without history of optic neuritis. They observed a delay in the a-wave and b-wave latencies in the combined rod-cone response in MS, while no difference was observed in ERG amplitudes between MS

without optic neuritis and controls. However, a significant reduction in ERG amplitudes were observed in MS with non-optic neuritis eyes during the follow-up period of three years, suggesting primary progressive functional loss in the outer retina[16].

Most studies revealed affection of the cone response or the combined rod-cone response without affection of the rod response. However, Gundogan et al.,2007, in agreement to our results, reported a significant delay in the latency of b- wave of the rod response (in addition to the a and b waves of combined rod cone response) between MS patients without a history of optic neuritis and controls[14]. Hence, the electrophysiological findings that revealed retinal damage as a consequence of myelin loss in the optic nerve, was also signifying an early feature of MS.

The absence of significant difference of the b-wave/ a-wave amplitude ratio between the MS and healthy control groups is not surprising because the amplitude of both a and b waves decreased and this goes with [7]. In contrast to our results, no abnormalities were observed in ff-ERG of MS patients in the study of Persson and Wanger, 1984[15]. These normal findings could be explained by the small sample size as the number of patients was 15 and the control was 10. Moreover, they did not use the ISCEV standards. The prolongation of ERG and mf-ERG peak times may indicate subclinical retinopathy possibly related to neuroinflammatory changes. Retinal periphlebitis has been reported in patients with MS, which was thought to be related to MS severity [17].

Anti-retinal antibodies have also been reported in cellular proliferative disorders and in the pathogenesis of autoimmune retinopathy. Autoantibodies that are directed against neuronal antigens may also play a key role in axonal injury in MS and may be responsible for the reduction in amplitudes identified in our electrophysiological studies [16]. This was supported by the observation of Forooghian et al., 2006 who found that patients with the highest antibody titers had abnormal ERG recordings [12]. Limitation: Our work has some limitations; firstly, the small sample size. Secondly, the study included patients with RRMS only and didn't include patients with SPMS or PPMS.

Conclusion

In conclusion, our study suggests the presence of functional and structural affection of the bipolar and the photoreceptors layers in the outer retina in optic neuritis and non-optic neuritis eyes of MS. Thus, the inner retinal layer does not influence the function of the outer retinal layer. Therefore, the outer retina could be a site for primary pathology in MS, unrelated to the optic nerve affection.

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Declarations

Ethics approval and consent to participate

The study protocol was approved by the Research Ethical Committee, Faculty of Medicine, Beni-Suef University, Egypt. We obtained informed consents from the patients and control prior to the study.

Consent for publication: Not applicable.

Competing interests

The authors declare that they have no competing interests.

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