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Correlation between Findings of Visual Evoked Potential and Optical Coherence Tomography of Macula and Optic Nerve Head in Patients with Multiple Sclerosis

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Abstract: Background: MS is an immune-mediated demyelinating and axonal damage of the central nervous system. Some recent models support the presence of two connected mechanisms, inflammation and neurodegeneration, taking place in MS. However, the temporal relationship between them remains unclear. Visual disturbances including blurred vision, visual field defects, and color desaturation are frequently occurring symptoms in MS and are assumed to be caused by inflammation in and axonal damage to the optic nerve as part of the CNS. Acute ON affects 50%–70% of MS patients. Visual dysfunction is one of the main causes of disability in MS. The retina is a good model for the study of neurodegeneration since it lacks myelin, meaning that changes in the RNFL thickness will be due only to axonal damage. Recently, numerous reports suggest that OCT parameters might detect and monitor axonal loss in MS patients. Some authors advocate OCT as a useful biomarker of disease activity and recommended that OCT should be part of the routine monitoring of patients with MS 54. Peri-papillary RNFL has been forefront among these parameters and thinning of the RNFL, demonstrated by OCT, became a strong evidence of axonal injury related to the inflammatory demyelination process in MS. The advancements in OCT technology enabled measurement of discrete retinal layer thicknesses. After that, the assessment of GCIPL has been advocated to be taken into consideration. **Aim of the study:** This prospective, evaluate the optical coherence tomography of macular ganglion cell layer (OCT GCL) and optical coherence tomography of optic nerve head (OCT ONH) in MS patients as markers of axonal loss and correlate between these findings and optic nerve function recorded by visual evoked potential VEP. **Patients and Methods:** This study is included 30 eyes of patients with clinically defined multiple sclerosis according to the revised McDonald criteria 2017. Patients were divided into two subgroups: MS with history of optic neuritis (MS-ON) and they were 15 eyes. The other group is MS without history of optic neuritis (MS-NON) and they were 15 eyes.10 eyes of disease-free controls were age and sex-matched to the MS patients **Results:** There were no significant differences regarding the age and gender distribution of posterior uveitis among patients. The mean age of the patients was 32 years (range 12 to 56 years) and of the controls was 33 years (range 15 to 53 years). Gender distribution was 19 males (13 patients & 6 controls) and 26 females (17 patients & 9 controls). In the study Optic nerve structure were assessed by OCT macula (GCL/IPL complex) and OCT ONH. There is significant reduction of average GCL thickness in MS patients more than control group cases of MS ON show significant reductions in average GCL/IPL complex thickness comparing with MS NON and control group. There is no significant reduction in average GCL/IPL complex thickness between cases of MS NON and control group Regarding average RNFL thickness, cases of MS show significant reduction in average thickness in comparison with Control group. Cases of MS ON show significant reductions in average RNFL thickness comparing with MS NON and control group. There is no significant reduction in average RNFL thickness between cases of MS NON and control group. Regarding VEP, p 100 peak time and N75 – p 100 amplitude are measured. p100 peak time shows significant delay in MS patients. This delay in MS ON more than MS NON and control group. with no significant delay in p 100 peak time between MS NON and control group. N75 – p 100 amplitude is significantly reduced in MS patients. **Conclusion:** There is no correlation between average GCL/IPL thickness or RNFL thickness and VEP either P100 peak time or N75-P100 amplitude in MS patients with and without optic neuritis.

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1. Introduction:

Multiple Sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system characterized by relapses in its early course and subsequent progression over time. The visual pathways are commonly involved in MS 1.

Optic neuritis (ON) is an acute inflammatory demyelinating disorder of the optic nerve. The general characteristics of ON include unilateral, and painful visual loss without systemic or other neurological symptoms and ON is mostly seen in young females. 2.

ON may be the initial presentation in about 20% of MS patients and ON presentation may occur during the course of the disease in 50% of patients with MS 2, 3.

Optical coherence tomography (OCT) is one of the most commonly used imaging modalities in ophthalmology. Since its appearance in 1991, OCT has developed greatly from Time domain TD-OCT to spectral domain SD-OCT 4.

OCT is a quick, sensitive, non-invasive, user-friendly device that provides high-resolution images of the peripapillary retinal nerve fiber layer (pRNFL), ganglion cell layer (GCL), and optic nerve head, yielding reproducible and reliable measurements 5.

Visual-evoked potentials (VEP) assess visual pathway functional integrity from the retina to the occipital cortex by measuring the latencies, amplitudes and symmetry of cortical responses to standardized visual stimuli6.

Visual pathways lesions can be detected by delayed visual-evoked potentials (VEP) latencies and decreased amplitude.7.

So, objective assessment of optic nerve structure (by OCT) and function (by VEP) complement each other. They can be used for assessment of CNS degeneration in MS patients.

2. Patients and Methods:

This study is prospective study which included 30 eyes of patients with clinically defined multiple sclerosis according to the revised McDonald criteria 2017. Patients were recruited from inpatient and outpatient clinics in Departments of Neuropsychiatry and Ophthalmology; Tanta University Hospitals from June 2018 to June 2019. Patients were divided into two subgroups: MS with history of optic neuritis (MS-ON) and they were 15 eyes. The other group is MS without history of optic neuritis (MS-NON) and they were 15 eyes.10 eyes of disease-free controls were age and sex-matched to the MS patients.

Inclusion criteria:

1. Patients diagnosed with Relapsing Remitting Multiple sclerosis (RRMS) diagnosed according to revised McDonald criteria 2017.
2. Age group above 18 years.
3. Patient with MS ON at least one month after resolving of attack.

Exclusion criteria:

Any systemic diseases or ophthalmological pathologies that could be associated with visual disorders like:

1. Patients with any media opacity as corneal opacity or dense cataract.
2. Patients diagnosed with any other retina disease as diabetic retinopathy, high myopia.
3. Patients diagnosed with any other optic neuropathy like glaucoma, compressive ON, etc.
4. Patients with other type of MS i.e progressive MS or patients with other demyelinating disease like Neuromyelitis optica (NMO) or acute disseminating encephalomyelitis (ADE).
5. Patients with acute attack of optic neuritis as ON head edema will prevent good measurement of RNFL.

Methods:

All patients were submitted to:

1- Detailed history taking (include age, sex, residence, onset and duration of MS, previous attacks of optic neuritis).

2- Visual acuity testing (uncorrected and best corrected) using logarithm of the minimal angle of resolution (long MAR) units.

3- Detailed anterior segment examination.

4- Fundus examination and intraocular pressure (IOP) measurement.

5- color vision.

Investigations:

1. **Optical coherence tomography (OCT GCL and RNFL):**

Nerve fiber layer imaging was done using the ZEISS Cirrus™ HD-OCT Model 4000 (Carl Zeiss-Meditec, Dublin, CA) which uses a super luminescent diode laser with a center wavelength of 840 nm. After pupillary dilation, three individual 200 x 200 cube optic disc scans were obtained with Cirrus OCT (software version 4). The minimum acceptable signal strength was 6. Peripapillary RNFL parameters evaluated were: average thickness (360°), temporal quadrant thickness (316° to 45°), superior quadrant thickness (46° to 135°), nasal quadrant thickness (136° to 225°) and inferior quadrant thickness (226° to 315°).

Macular scanning using the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) macula 200×200 acquisition protocol. The ganglion cell analysis (GCA) algorithm was used to detect the macular GCIPL and to measure the thickness of the overall average, minimum, superotemporal, superior, superonasal, inferonasal, inferior, and inferotemporal GCIPL.

2. Visual evoked potential.

VEPs P100 peak time and N75 – P100 amplitude

were recorded using RETIMAX by CSO (Scandicci, Florence, Italy). VEP recordings were performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines8. The reference electrode was placed on the midline frontal point (Fz), an active electrode on the midline at the occipital region (Oz according to the 10–20 system), and the ground electrode on the forearm. needle electrodes were used and their impedance was maintained below 5 k Ohm.

The stimuli were presented uni-ocularly. A hundred responses were averaged in each run and two runs were performed for each eye. The peak time and amplitude ("peak to peak") of the P100 component were determined for each eye. Normative value was 100 ± 10 ms for VEP p100 peak time and ≥ 5 µV for VEP amplitude.

Statistical analysis

The analysis was calculated by SPSS version 25 (SPSS Inc., Chicago, IL). Furthermore, the qualitative parameters were described by number of frequency and percentage while the quantitative variables were described by mean, standard deviation and range.

In addition, the comparison of two dependent quantitative variables was calculated by T paired test while the comparison of two independent quantitative variables was calculated by T test. On the other hand, the comparison of two nonparametric variables was calculated by Mann-Whitney U test.

Comparison between three independent variables was calculated by ANOVA test with a post hoc analysis.

However, comparison between two qualitative variables was done by Chi square test. The correlation was done by Pearson test.

3. Results:

The clinical characteristics of the MS patients and control groups are shown in table 1 and because cases and controls were age and sex matched, there were no statistically significant differences in these descriptive characteristics. Mean ages in the MS ON, MS NON and control groups were 31.87 years (range 21– 60 years), 26.8 years (range 19-36 years) and 28.2 years (range 27-29 years) respectively. Disease duration was 41.93 ± 59.34 months in MS ON and 34.6 ± 64.24 months In MS NON. Women represented 73.33% of subjects in MSON and 86.67% in MS NON and 40 % in Control group.

Table (1): Characteristics of Patients with multiple sclerosis (MS) and disease-free controls

	MS with optic neuritis N=15	**MS without optic neuritis N=15**	**Control N=10**	**F**	**P Value**
	Mean ± SD (Range)	**Mean ± SD (Range)**	**Mean ± SD (Range)**		
Age (years)	31.87 ± 12.79 (21 – 60)	26.8 ± 5.94 (19 – 36)	28.2 ± 0.78 (27 – 29)	1.34	0.274
	Mean ± SD (Range)	**Mean ± SD (Range)**	**Mean ± SD (Range)**	T	**P Value**
Duration of disease (months)	41.93 ± 59.34 (4 – 180)	34.6 ± 64.24 (4 – 192)		0.325	0.748
	Frequency %	**Frequency %**	**Frequency %**	**X2**	**P Value**
Male	4 (26.67%)	2 (13.33%)	6 (60%)	6.349	0.069 Calculated by Monte Carlo
Female	11 (73.33%)	13 (86.67%)	4 (40%)		
Right eye	8 (53.33%)	7 (46.67%)	5 (50%)	0.133	0.936
Left eye	7 (46.67%)	8 (53.33%)	5 (50%)		

Optic nerve structure were assessed by OCT macula GCL/IPL complex and OCT ONH. optic nerve function was assessed by visual evoked potentials (VEPs) (p100 peak time and amplitude)

There is significant reduction of average GCL thickness in MS patients more than control group (p > 0.001) as shown in table 2 figure 17. When MS ON and MS NON patients were analyzed and compared with control group, cases of MS ON show significant reductions in average GCL/IPL complex thickness comparing with MS NON and control group (p > 0.001). There is no significant reduction in average GCL/IPL complex thickness between cases of MS NON and control group (P = 0.071) (Table 3).

Regarding average RNFL thickness, cases of MS show significant reduction in average thickness in comparison with Control group (P >0.001) (Table 2). Cases of MS ON show significant reductions in average RNFL thickness comparing with MS NON and control group (p > 0.001). There is no significant

reduction in average RNFL thickness between cases of MS NON and control group (P= 0.711) (Table 3) (Figure 1).

Regarding VEP, p 100 peak time and N75 – p 100 amplitude are measured. p100 peak time shows significant delay in MS patients (P = 0.001) (Table 2).

This delay in MS ON more than MS NON and control group (p > 0.001) table 3. with no significant delay in p 100 peak time between MS NON and control group (p = 0.21) table 3. N75 – p 100 amplitude is significantly reduced in MS patients (P = 0.005) (Table 2). particularly in MS ON more than MS NON and control groups (p > 0.001) with no significant reduction in N75 – p 100 amplitude between M NON and control group (Table 3)

Table (2): Comparison between functional and structural measurements in control eyes and MS eyes.

	Patient with multiple sclerosis N=30	**Control N=10**	T	P Value
	Mean ± SD (Range)	**Mean ± SD (Range)**		
Average GCL/IPL thickness (µm)	68.9 ± 11.38 (52 – 91)	83.6 ± 6.2 (72 – 88)	-3.88	<0.001*
Average RNFL thickness (µm)	78.8 ± 12.58 (55 - 105)	90 ± 8.2 (76 – 98)	-3.22	<0.004*
VEP P100 peak time (msec)	7.79 ± 2.9 (3.4 – 12)	9.54 ± 0.78 (8.26 – 10.34)	-1.85	0.005*

Table (3): Comparison of functional and structural measurements in control eyes and MS eyes with and without optic neuritis

	(MS ON) N=15	**(MS NON) N= 15**	**Control N=10**	**F**	**P Value**	**Post Hoc Test**
	Mean ± SD (Range)	**Mean ± SD (Range)**	**Mean ± SD (Range)**			
Average GCL/IPL thickness (µm)	62.2 ± 9.73 (52 – 84)	75.53 ± 8.87 (59 – 91)	83.6 ± 6.2 (72 – 88)	19.76	<0.001*	P1 <0.001* P2 <0.001* P3 0.071
Average RNFL thickness (µm)	70.67 ± 10.39 (55 – 91)	87 ± 8.77 (73 – 105)	90 ± 8.21 (76 – 98)	16.999	<0.001*	P1 <0.001* P2 <0.001* P3 0.711
VEP P100 peak time (msec)	131.79 ± 19.03 (120 – 180.2)	105.1 ± 9.98 (92.4 – 129)	95.57 ± 2.46 (92.58 – 99.61)	25.819	<0.001*	P1 <0.001* P2 <0.001* P3 0.21
N 75 – p 100 amplitude (mv)	5.22 ± 1.61 (3.41 – 10.54)	10.36 ± 1.02 (8 – 12)	9.54 ± 0.78 (8.26 – 10.34)	72.468	<0.001*	P1 <0.001* P2 <0.001* P3 0.249
P1 Comparison between MS with optic neuritis and MS without optic neuritis P2 Comparison between MS with optic neuritis and Control P3 Comparison between MS without optic neuritis and Control						

There is no correlation between average GCL/IPL thickness or RNFL thickness and VEP either P100 peak time or N75-P100 amplitude in MS patients with and without optic neuritis. (Table4) (Table5) (Fig1) (Fig 2).

Table (4): Correlation between OCT with VEP results in (MS with ON)

	VEP P 100 (n=15)		**VEP Amplitude (n=15)**	
	R	**P**	**R**	**P**
ONH average	-0.144	0.61	0.289	0.296
GCL/IPL	-0.313	0.255	0.289	0.296

Table (5): Correlation between OCT with VEP results in (MS without ON)

	VEP P 100 (n=15)		**VEP Amplitude (n=15)**	
	R	**P**	**R**	**P**
ONH average	**-0.302**	**0.294**	**0.562**	**0.029***
GCL/IPL	**-0.468**	**0.09**	**0.216**	**0.439**

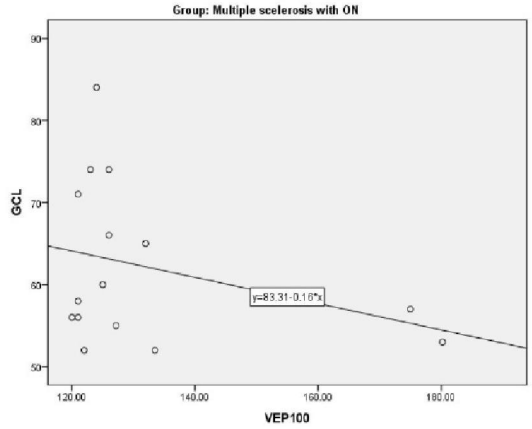

Figure (1):correlation between average GCL thickness and VEP p100 peak time in MS ON.

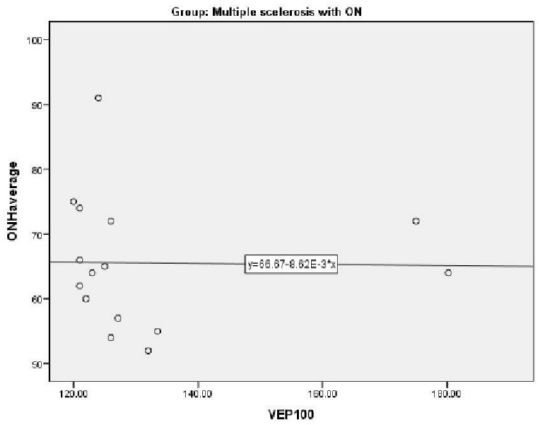

Figure (2): correlation between average RNFL thickness and VEP p100 peak time in MS ON.

4. Discussion:

In our study there is significant reduction of average thickness of GCL in MS patients in comparison with control group. (p> 0.001). MS ON patients show significant reduction in GCL thickness in comparison with MS NON and Control group (P >0.001). MS NON also show reduction in average GCL thickness but with no significance (p = 0.07).

Our result regarding GCL thickness in MS ON coincide with results of **Balk et al** 9, **B. Syc et al** 10, **Schneider et al** 11, **Huang-Link et al** 12. They stated that the RNFL and GCL were thinner in MS patients, but the change was more pronounced in MS ON.

Our result regarding GCL thickness in MS NON shows thinning of GCL with little significance. This coincides with results of **Modvig et al 13**, **Huang-Link et al** 12 and **Oberwahrenbrock et al** 14, however **Balk et al** 9 and **B. Syc et al** 10, **Schneider et al** 11 results are in contrary to our results. This could be explained by their large sample of patients, also all our patients are under treatment which may delay the subclinical thinning.

In our study we have found that change in GCL in MS patients (P >0.001) especially ON patients is more than change in RNFL (P >0.004). This confirms **Britz et al** 15 and **Saidha et al** 16 results that showed GCL thinning is prior to RNFL thinning and more severe.

According to our result we have found significant reduction in average RNFL thickness in MS patients in comparison with control group as shown in table 4 (P > 0.001). These data are supported by previous study done by **Henderson et al** 17. Cases of MS ON show significant reductions in average RNFL thickness comparing with MS NON and control group (p > 0.001). Our results of RNFL reduction in MS-ON patients are coinciding with the findings of **Fisher et al** 18. which showed significant RNFL thinning in this population compared with the control group. **Costello et al** 19 found thinning of the RNFL thickness measured by OCT in 74% of patients with optic neuritis.

In our study there is reduction in average RNFL thickness in MS NON patients in comparison with control group but with no significance (P <0.05). our result is coinciding with **Siger et al** 20 and **Trip et al** 21, but is in contrary with results of **Fisher et al** 6 and **Sepulcre et al** 22. This can be explained by that our study was on only 15 eyes of MS NON, however **Fisher et al** 18 studied about 180 eyes of MS patients and **Sepulcre et al** 22 studied also about 122 eyes of MS patients which is large sample of patients.

Regarding P100 peak time, MS ON show significant delay more than MS NON patients and control group. MS ON also show reduction in N75-p100 amplitude more than MS NON patients and control group. these finding agree with finding of previous study of **Parisi et al** 23 who examined 14 eyes of MS ON a significant reduction in NFL thickness in. pattern electroretinogram and VEP showed a significant delay in latency and reduction in amplitude.

In our study there is no correlation between average GCL/IPL thickness or RNFL thickness and VEP either P100 peak time or N75-P100 amplitude in MS patients. our results agree with **Parisi et al** 23 and **Gundogan et al** 24 results which stated that no correlation between VEP changes and NFL thickness. **Parisi et al** 23 stated that no correlation between VEP changes and NFL thickness in MS ON patients, however there is a correlation between PERG changes and NFL thickness. **Gundogan et al** 24 showed no correlation between RNFL thickness and P100 peak time in MS NON patients. Our results are in contrary with **Trip et al** 21 who found that there is correlation between RNFL thickness and P100 amplitude. The

difference may be due to sample characteristics there study was on patients of optic neuritis generally not specified to MS and relatively larger sample. **Pueyo et al** 25 found that RNFL thickness correlated with both P100 latency and amplitude. this could be explained by their large sample (25 eyes with MS ON) and that their study include all MS patient not only Remitting Relapsing type.

Conclusion:

SS-OCT yields reasonable amount of data regarding morphological changes of the vitreoretinal interface, retina, and choroid in acute posterior uveitis. Unlike ordinary OCT, SS-OCT with longer wavelength enables better wider field imaging of deeper structure and improves detection of the choroid-sclera border with greater sensitivity at scanning the deep choroidal structures and the superficial retinal layers in the same image.

SS-OCT is quick, easy, noninvasive tool and can be performed repeatedly without any complications. As well, SS-OCT is superior and more sensitive for revealing the distribution of fluid and morphology of uveitic macular edema (UME) with great ability to detect minimal subretinal fluid., The results of SS-OCT are also quantitative, and thus it can be performed to evaluate the activity of posterior uveitis and to quantify the degree of inflammation. However, it does not mean that SS-OCT can completely replace the role of FFA in the patients with posterior uveitis as SS-OCT cannot provide the underlying retinal vascular status.

In SS-OCT, enhanced visualization and *in vivo* measurement of retinal and choroidal thickness are allowed and that is important in diagnosis of active posterior uveitis. An additional important SS-OCT finding in posterior uveitis is the integrity of photoreceptors and RPE which may predict the prognosis of the condition and the response to treatment. Moreover, SS-OCT can allow detection of disease complications as ERM, VMT, MH, CNV or foveal atrophy.

Interestingly, retinal and choroidal thickness may be promising parameters that can be used to characterize different disease entities and monitor resolution of posterior pole inflammatory disorders and efficacy of treatment. Also, they may potentially be useful in predicting prognosis of condition.

Furthermore, increased retinal and choroidal thickness may be a clue for detection of subclinical inflammatory activity of the retina and choroid during the quiescent phase, which could exacerbate, leading to an acute recurrent attack of uveitis.

Additionally, SS-OCT can be used to correlate the morphologic changes of macula, retinal and choroidal thickness with VA in patients with posterior uveitis. Thus, serial imaging of the macula and correlation with change in VA may help to predict the prognosis and allow for more accurate follow-up of response to treatment.

In this respect, SS-OCT (in the appropriate clinical context) may add a great deal of information not only in the diagnosis, but also in management and follow-up of the inflammatory process of the retina and choroid in posterior uveitis. As well, it could be used as an adjunctive tool for screening of certain posterior uveitis entities.

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