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RESEARCH ARTICLE

DIFFUSION TENSOR IMAGING OF OPTIC RADIATION IN MULTIPLE SCLEROSIS: CORRELATION WITH VEP.

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Abstract

Purpose: To test the significance of FA and MD of diffusion tensor imaging in differentiating MS patients with normal and delayed VEP
Material and Methods: This study was conducted upon 70 patients (aged 18-46 years: mean 32years) with multiple sclerosis that underwent diffusion tensor imaging and VEP. The average fractional anisotropy (FA) and mean diffusivity (MD) value of the right and left optic radiation in patients with normal (n=39) and delayed (n=28) were calculated and correlated with VEP of both sides. The receiver operating characteristic curve was drawn to detect the cutoff point of FA and MD of optic radiation used to differentiate patients with normal and delayed VEP. Correlation between FA, MD of OR with VEP, disease duration and EDSS were tested by person correlation coefficient. Also inter-observer agreement was done by comparing the FA and MD obtained by the two observers. A P value less than 0.05 was considered statistically significant.
Results: The mean FA of optic radiation in patient with delayed VEP (0.36 ± 0.03 and $0.36 \pm 0.08 \times 10^3 \text{mm}^2/\text{s}$ first and second observer respectively) was significantly lower than the mean FA of optic radiation in patient with normal VEP (0.39 ± 0.03 and $0.39 \pm 0.04 \times 10^3 \text{mm}^2/\text{s}$ first and second observer respectively). The mean MD of optic radiation in patient with delayed VEP (0.96 ± 0.06 and $0.98 \pm 0.07 \times 10^{-3} \text{mm}^2/\text{s}$ first and second observer respectively) was significantly higher than the mean MD of optic radiation in patient with normal VEP (0.88 ± 0.05 and $0.89 \pm 0.05 \times 10^{-3} \text{mm}^2/\text{s}$ first and second observer respectively). Selection of FA of ≤ 0.38 and $\leq 0.395 \times 10^3 \text{mm}^2/\text{s}$ (first and second observer respectively) to differentiate patient with delayed and normal VEP has an area under the curve of 0.804 and 0.734, a sensitivity of 75% and 82.1%, a specificity of 82.1% and 56.4%, and accuracy of 79.1% and 67.16%, respectively. Selection of MD of ≥ 0.885 and $\geq 0.90 \times 10^{-3} \text{mm}^2/\text{s}$ (first and second observer respectively) to differentiate patient with delayed and normal VEP has an area under the curve of 0.901 and 0.893, a sensitivity of 96.4% and 92.9%, a specificity of 76.9% and 71.8%, and accuracy of 85.07% and 80.6% respectively.

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Conclusion: Diffusion tensor imaging is a non-invasive promising method that can use for differentiating patients of MS with normal and delayed VEP.

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Introduction:-

Multiple sclerosis:-

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS), which results in axonal degeneration. The afferent visual pathway, from retinal photoreceptor cells to visual cortex area neurons, is the most frequently affected white matter pathway in central nervous system (CNS) inflammatory disorders. Optic neuritis (ON) is an inflammatory demyelinating disease and the presenting symptom in 20% of MS patients and about 40% of patients will develop ON during the course of MS (1). Recovery after ON is often incomplete with at least one-third of patients having persistent visual symptoms, which may lead to a reduced quality of life (2).

The diffuse neurodegeneration may lead to the degradation of visual system structures and functions and may contribute to the global and focal disease burden in MS. Therefore, a quantitative and precise assessment of microstructural damage in the visual pathway would enhance our understanding of disease pathology in MS (3).

Optical Coherence Tomography (OCT):-

Optical Coherence Tomography (OCT) has been reported as a noninvasive, safe, and easy technique that uses near infrared light to function. OCT studies have demonstrated the thinning of RNFL in patients with a prior history of ON, as well as in patients with MS (4). Previous studies have proposed the use of OCT to differentiate MS subtypes, to evaluate disease activity, or to estimate the efficacy of neuroprotective treatment (5).

VEP:-

The cortical visual evoked potential (VEP) is an established method for assessing visual pathway function. Pattern VEP is generally used for the detection of visual function disability (demyelination disease, optic neuritis, ischemic optic neuropathy, compressive optic neuropathy, and amblyopia) and objective visual acuity assessment (visual function for children, malingering, and psychogenic visual disability) (6).

EDSS:-

The Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis and monitoring changes in the level of disability over time. It is widely used in clinical trials and in the assessment of people with MS. The scale was developed by a neurologist called John Kurtzke in 1983 as an advance from his previous 10 step Disability Status Scale (DSS) (7).

MRI:-

Parameters based on routine structural magnetic resonance imaging (MRI), such as T2 lesions and gadolinium (Gd) –enhancing plaques, represent highly relevant biomarkers for diagnosis and therapy response in randomized controlled clinical trials (8), but they provide insufficient information on functionally relevant disease severity, especially with respect to the visual system (9).

Diffusion tensor imaging(DTI):-

Diffusion tensor imaging is an emerging MR imaging technique which reflects micro-movement of water molecules and can distinguish between different tissue compartments at the cellular level with different metrics. The most common metrics of diffusion tensor imaging used are fractional anisotropy (FA) and mean diffusivity (MD). DTI facilitates the reconstruction and investigation of the optic radiation and allows in vivo anatomical assessment of damage-dysfunction relationships. The multimodal use of DTI together with optical coherence tomography (OCT) and visual evoked potentials (VEP) facilitates an objective assessment of the entire afferent visual system and provides a symptom-based clinical evaluation with new promising outcome parameters in therapeutic phase II and phase III neuroimmunological disease studies, especially of remyelinating and neuroprotective agents (10).

The aim of this work was to test the significance of FA and MD of diffusion tensor imaging in differentiating MS patients with normal and delayed VEP.

Material And Methods:-

Patients:-

Institutional review board approval was obtained (NO.) This study was a prospective study that was performed on 70 consecutive patients diagnosed with multiple sclerosis. Informed consent was taken from each patient. **Inclusion criteria** were patients diagnosed with multiple sclerosis according to modified McDonald criteria 2017. Exclusion criteria were patients with history of stroke, epilepsy or neurodegenerative disorders. Two patients were **excluded** from the study due to motion artifacts. The final patients included in this study were 68 patients (28 male and 40 female, age ranged from 18-46 years; mean age 32 years). All patients underwent diffusion tensor imaging of the brain, VEP, EDSS.

VEP:-

In all cases, one skilled test conductor measured VEP (RetiSystem; Roland Consult Instrument GmbH, Wiesbaden, Germany) based on the International Society for Clinical Electrophysiology of Vision recommendations. To examine pattern VEP, subjects were seated in a comfortable posture and were instructed to maintain fixation at the center of the stimulus located at a distance of 100 cm on a 20 × 30 cm black-and-white video display monitor. The stimulus consisted of a 16 × 16 lattice with a pattern reversal rate of 1.3 times per second and band filter from 0.5 to 100 Hz. The test was conducted by applying the visual stimulus alternately to both eyes. Fixation stability of the eyes was monitored closely by an experienced electrophysiology technician.

EDSS:-

The EDSS scale ranges from 0 to 10 in 0.5 unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist. EDSS steps 1.0 to 4.5 refer to people with MS who are able to walk without any aid and is based on measures of impairment in eight functional systems (FS): (1) Pyramidal : weakness or difficulty moving limbs (2) Cerebellar : ataxia, loss of coordination or tremor (3) Brainstem : problems with speech, swallowing and nystagmus (4) Sensory : numbness or loss of sensations (5) Bowel and bladder function (6) Visual function (7) Cerebral (or mental) functions (8) Other.

MR imaging:-

All patients were examined on a 1.5-tesla scanner (Ingenia, Philips, Philips Medical Systems, Best, Nederland). A self-shielding gradient set with a 16-channel neurovascular coil were used. Sequences used: T1-weighted images (TR/TE = 800/15 ms), T2-weighted fast spin-echo images (TR/TE = 6000/80 ms) and Fluid-attenuated inversion recovery FLAIR images. The scanning parameters were section thickness = 5 mm, an inter-slice gap = 1.5 mm, a field-of-view (FOV) = 25-30 cm² and an acquisition matrix = 256 X 224. DTI acquired using a single-shot echo-planar imaging sequence (TR/TE = 3200/ 90 ms) with parallel imaging (SENSitivity Encoding [SENSE] reduction factor P 2). Automatic multi-angle-projection shim and chemical shift selective fat suppression (CHESS) technique applied to reduce the artifacts at diffusion-weighted MR images. Diffusion gradients were applied along 32 axes, using a *b*-value of 0 and 1000 s/mm². The scanning parameters were: FOV = 250 × 170 mm², data matrix = 92 × 88 and voxel dimensions = 2.43 × 2.54 × 2.5 mm³. Forty-eight slices were obtained, with a thickness of 2.5 mm, with no gap and the total scan duration was 7-8 minutes. Diffusion tensor imaging was performed before contrast medium injection.

Image analysis:-

Image analysis was performed by two neuro-radiologist observers who were blinded to the clinical tests. Fiber tracking of the optic radiation was done bilaterally. A ROI was placed on the obtained tracks, the FA and MD on the right and left side were calculated according to previously described equation.

Statistical analysis:-

The statistical analysis of data was done by using Statistical Package for Social Science version 21 (SPSS Inc., Chicago, Ill, USA). Our cases were classified into two group: delayed (diseases) and normal (control) groups. All continuous data was tested for their normality. The mean and standard deviation of FA and MD values of both optic radiations obtained by both observers, disease duration, VEP and EDSS results for both study groups were calculated. The analysis of data was done to test the statistically significant difference. Student t-test was used to compare between the FA, MD, of delayed and normal VEP groups. The receiver operating characteristic curve (ROC) was drawn to detect the cutoff point of FA and MD value of optic radiation used to differentiate normal and delayed VEP. Correlation between FA, MD of OR with VEP, disease duration and EDSS were tested by person

correlation coefficient. Also inter-observer agreement was done by comparing the FA and MD obtained by the two observers. A *P* value less than 0.05 was considered statistically significant.

Results:-

Demographics:-

The mean FA of optic radiation in patient with delayed VEP (0.36 ± 0.03 and $0.36 \pm 0.08 \times 10^{-3} \text{mm}^2/\text{s}$ first and second observer respectively) was significantly lower than the mean FA of optic radiation in patient with normal VEP (0.39 ± 0.03 and $0.39 \pm 0.04 \times 10^{-3} \text{mm}^2/\text{s}$ first and second observer respectively). The mean MD of optic radiation in patient with delayed VEP (0.96 ± 0.06 and $0.98 \pm 0.07 \times 10^{-3} \text{mm}^2/\text{s}$ first and second observer respectively) was significantly higher than the mean MD of optic radiation in patient with normal VEP (0.88 ± 0.05 and $0.89 \pm 0.05 \times 10^{-3} \text{mm}^2/\text{s}$ first and second observer respectively).

Selection of FA of ≤ 0.38 and $\leq 0.395 \times 10^{-3} \text{mm}^2/\text{s}$ (first and second observer respectively) to differentiate patient with delayed and normal VEP has an area under the curve of 0.804 and 0.734, a sensitivity of 75% and 82.1%, a specificity of 82.1% and 56.4%, and accuracy of 79.1% and 67.16%, respectively.

Selection of MD of ≥ 0.885 and $\geq 0.90 \times 10^{-3} \text{mm}^2/\text{s}$ (first and second observer respectively) to differentiate patient with delayed and normal VEP has an area under the curve of 0.901 and 0.893, a sensitivity of 96.4% and 92.9%, a specificity of 76.9% and 71.8%, and accuracy of 85.07% and 80.6% respectively.

There was negative and positive correlation between the FA and MD of first and second observers with the VEP respectively with *P* value .001 and .001 respectively, while there was no correlation between the DTI measurement and disease duration or the EDSS.

There was positive correlation and inter-observer agreement in FA and MD reading between the first and second observers with *P* value equal .000 for both.

Discussion:-

DTI metrics have been used to monitor structural changes that occur during the course of MS in both WM and GM due to their marked sensitivity in detecting structural tissue abnormalities in the course of MS, DTI parameters also can be used as prognostic markers of disease evolution (11). In this study, combined FA and MD are found to be accurate parameters for differentiating MS patients with normal and delayed VEP (with affected visual pathways).

Fractional anisotropy (FA) is a common measurement used in DTI studies that indicates the orientation of diffusion and is high along well-defined pathways such as the corpus callosum, pyramidal tracts, and optic radiations. A reduction in FA in such pathways is therefore a potential marker of axonal structural integrity (12) (13). In our study we found that mean FA of optic radiation in patient with delayed VEP (was significantly lower than the mean FA of optic radiation in patient with normal VEP with negative correlation between FA and VEP. This was in agreement with Cross-sectional assessment (TBSS analysis) of the OR revealed correlations between the decrease of OR FA values and RNFL thinning in MS (14). Another studies showed negative correlations between mean P100 VEP and FA decline (15) (16) suggesting putative underlying anterograde trans-synaptic degeneration in the visual pathway to occur and to be quantifiable by OR DTI measurements. Whereas one study showed OR FA to be altered in ON patients compared to non-ON patients (17) another study found no changes in all OR DTI indices between the ON and non-ON group, at all (18).

The mean MD of optic radiation in patient with delayed VEP in our results was significantly higher than the mean MD of optic radiation in patient with normal VEP positive correlation between MD and VEP. This was coping with another studies shows that shows increased RD, MD, and AD values were positively correlated with VEP latency delay, FA showed negative correlations indicating an FA decrease to be associated with higher VEP latency delays (19)(20)(16). There was a highly significant correlation in the ROIs along the skeleton corresponding to the optic radiation between mean RD and mVEP, a highly negative correlation between mean FA and mVEP, and no correlation between mean AD and mVEP (15).

The integration of both DT- and conventional MRI measures together with connectivity-based regional assessment and the development of novel image analysis and visualization techniques could provide better means to understand

the nature and the location of WM abnormalities. The relationship between WM disruption, WM connectivity, and clinical measures will potentially allow clinicians to better correlate fiber tract disruption and MS symptoms such as cognitive impairment. Furthermore, it would ultimately lead to improved monitoring of patients, better prediction of the course of the disease, and more rapid assessment of new treatments or therapies

Limitation:-

For consolidation of our study results, further research should be applied on higher MRI magnetic field like 3 T machine, conducted to large number of cases, correlated results with other visual pathway results as well as patient prognosis and follow up

Conclusion:-

We concluded that combined FA and MD can differentiate MS patients with normal and delayed VEP i.e patients with affected visual pathway.

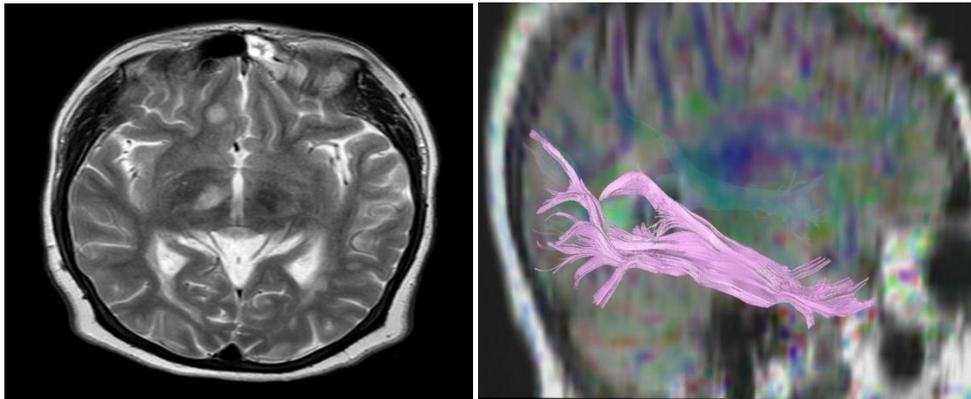


Figure 1:- Patient with multiple sclerosis and abnormal VEP. (a) axial T2WI: plaque of abnormal bright SI are seen in the right frontal lobe and right thalamus. (b) sagittal Diffusion tensor imaging of optic radiation in the same patient

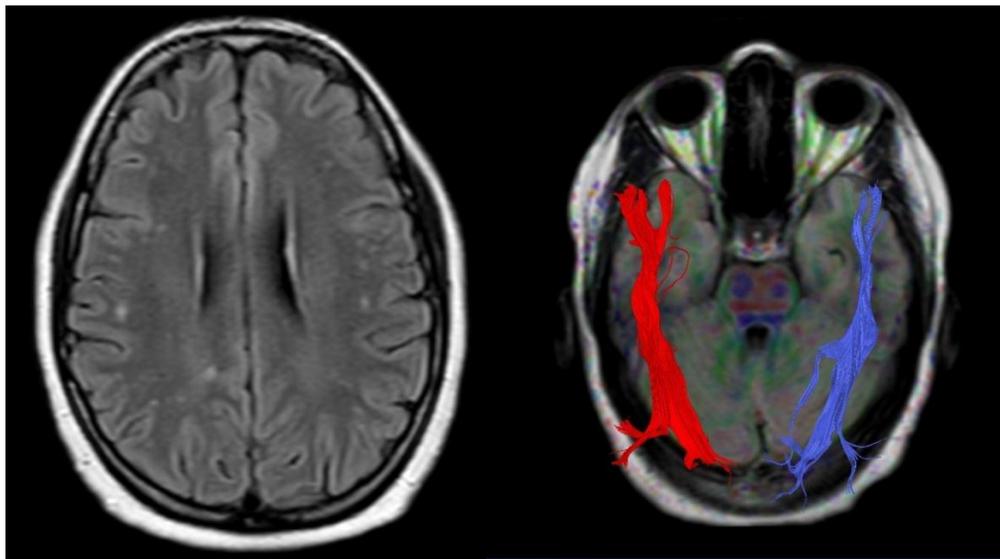


Figure 2:- Patient with multiple sclerosis and normal VEP. (a) axial FLAIR: plaque of abnormal bright SI are seen in the subcortical U fiber of both parietal lobes. (b) axial Diffusion tensor imaging of normal optic radiation on both sides in the same patient

Table 1:-Mean, standard deviation, minimum, maximum, of FA and MD ($10^{-3}\text{mm}^2/\text{s}$) of optic radiation in normal and decreased VEP

Pathology	Decreased VEP	Normal VEP	t test
FA			
First observer	0.36±0.03 (0.3-0.43)	0.39±0.03(0.31-0.44)	P<0.001*
Second observer	0.36±0.08(0.00-0.45)	0.39±0.04(0.32-0.47)	P=0.005*
MD			
First observer	0.96±0.06(0.88-1.06)	0.88±0.05(0.83-1.02)	P<0.001*
Second observer	0.98±0.07(0.89-1.12)	0.89±0.05(0.79-1.03)	P<0.001*

FA: Fractional Anisotropy, **MD:** Mean Diffusivity, **VEP:** visual evoked potential, **t test:** student t test.
*Statistically significant(p<0.05)

Table 2:-Results of ROC curve with calculation of AUC, accuracy, sensitivity, and specificity of FA and MD ($10^{-3}\text{mm}^2/\text{s}$) of the optic radiation used to differentiate patients with delayed and normal VEP

Parameter	Cut of Point	AUC	Sensitivity	Specificity	PPV%	NPV%	Accuracy
FA							
First observer	≤0.38	0.804	75	82.1	75	82.1	79.1
Second observer	≤0.395	0.734	82.1	56.4	57.5	81.5	97.16
MD							
First observer	≥0.885	0.901	96.4	76.9	75	96.8	85.07
Second observer	≥0.90	0.893	92.9	71.8	70.3	93.3	80.6

Table 3:-Correlation of FA and MD of the optic radiation with VEP, disease duration and EDSS

		FA		MD	
		1st observer	2nd observer	1st observer	2nd observer
VEP (P100 LATENCY)	r	-.611**	-.389**	.650**	.622**
	p	.000	.001	.000	.000
Disease duration (years)	r	-.027	-.141	.138	.087
	p	.828	.256	.267	.486
EDSS	r	-.102	-.162	.214	.141
	p	.411	.189	.082	.256

r: Pearson correlation coefficient

*statistically significant (p<0.05)

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