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Original Research Article

Diffusion tensor imaging in assessment of demyelinating diseases of central nervous system

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ABSTRACT

Background: Conventional MR plays an important role in detection of demyelinating lesions. Involvement of the lesion core, perilesional region and normally appearing white matter (NAWM) cannot be quantified using routine T2/FLAIR sequences. DTI is an important tool in assessment of anisotropy in affected and apparently normal region of brain. 3D Tractography maps are useful in showing white matter fibre loss. Aim was the assessment of white matter damage and neuroaxonal loss using DTI in demyelinating lesions

Methods: Cross sectional observational study including clinically suspected 30 patients of demyelinating disease. Patients were studied in 3Tesla Siemens Skyra MRI scanner with phased array coils. T1w, T2w, FLAIR, DWI, DTI, post contrast T1w images were included and FA, ADC, Tractography maps were generated. ANOVA test and BONFERONI analysis were used.

Results: We found mean FA of core lesion was 0.307±0.06, of perilesional region 0.444±0.03 and NAWM 0.567±0.06. The mean ADC value of core of the lesion was 1.24×10-3mm^2/sec±0.11×10-3mm^2/sec, perilesional region 1.16×10-6mm^2/sec ±0.1×10-3mm^2/sec and NAWM 1.04×10-3mm^2/sec±0.06×10-3mm^2/sec.

Conclusions: DTI is a useful MR technique that allows quantification of extent of demyelination in the white matter measuring FA and ADC values. The FA values which denote diffusivity and directionality are more reliable marker of demyelination compared to ADC values. DTI Tractography shows white matter tract disruption which may play role in assessing clinical outcome of patients.

Keywords: Apparent diffusion coefficient**,** Diffusion tensor imaging, Fractional anisotropy, Normally appearing white matter

INTRODUCTION

Demyelinating disorders are immune mediated conditions characterized by preferential destruction of central nervous system (CNS) myelin.[1] Broadly demyelinating diseases are divided into two groups- primary and secondary. Primary demyelinating diseases, denotes autoimmune mediated destruction of myelin sheath.[2] In contrast, secondary demyelinating disorders represent a spectrum of white matter disease characterized by damage to neurons or axons with the resultant breakdown of myelin.[3,4] Conventional MR scanning offers the most sensitive way to detect demyelinating lesions.[5]

DTI is acquired with diffusion weighting gradients that allows construction of a tensor, which can be used to produce images of both apparent diffusion co-efficient (ADC) and fractional anisotropy (FA), which demonstrate differences in the magnitude and directionality of water diffusion. DTI may provide information about tissue microstructure and architecture including size, shape, and organization and in turn

constitutes a proved and effective quantitative method for evaluating tissue integrity at a microscopic molecular level.[6]

METHODS

The study was Cross sectional Observational study and comprised 30 patients which was conducted in 18 months .We also studied 30 control subjects. Clinically suspected cases of Demyelinating diseases of brain and spinal cord based history, signs and symptoms irrespective of age and sex were included in the study. Patients with contraindications to contrast material and patients with implanted cardiac pacemaker or defibrillator were excluded from the study. MRI scan was performed using Siemens Skyra 3 Tesla MR System, using appropriate phased array coils. All patients of demyelinating diseases of CNS underwent MR examination of brain and spine. The Following MR sequences were used-T1 weighted, T2 weighted axial images, FLAIR axial images, DW images with b values of 0,500 and 1000, Diffusion Tensor images including FA and ADC maps (single shot SE-EPI sequence, matrix 128×128, b value 0-1000 m^2/s, 30 diffusion sensitive gradients). Post processing Diffusion tractography maps were generated. Data was analysed by standard statistical methods using ANOVA test and BONFERRONI analysis.

RESULTS

Fractional Anisotropy (FA) values

FA values are plotted at the core of lesion, perilesional region and normally appearing white matter (NAWM) in all of the patients in the present study. Mean FA values of core of the lesion were measured in all of the cases. Minimum FA value was obtained in patient of PML with HIV encephalopathy (0.17), maximum FA value was found in RNMO (0.342). Mean FA in RRMS cases was 0.289. In cases of PML, mean FA values were found lower in cases associated with IRIS and HIV encephalopathy. The mean FA was found lower (0.311) in case of SACD with concomitant Vit-B12 and copper deficiency than isolated cobalamine deficiency (0.341). Mean FA value of core of lesion in the study was 0.291(SD=0.046). FA values were plotted in the perilesional regions in all cases. Minimum FA (0.399) was found in case of PPMS and maximum value was found in Wernickes' encephalopathy (0.52). FA values were plotted in NAWM. FA values were measured at same regions of contralateral white matter wherever possible. However it was not possible in cases with extensive white matter involvement. Highest value was found in ADEM (0.698) and lowest value was found in RNMO (0.497).

Apparent diffusion co-efficient (ADC) values

ADC values obtained from the same regions with FA. Highest mean ADC (core) value was found in RNMO cases (1.55×10-3mm^2/sec) and lowest mean ADC value was found in PML cases (1.1×10-3mm^2/sec). The mean ADC value of all cases was found to be 1.24×10-3mm^2/sec (SD=0.11×10-3mm^2/sec). Mean ADC of RRMS cases was 1.26×10-3mm^2/sec. There was no significant difference found in ADC values of core of PML and PML-IRIS cases.($p>0.05$) Highest mean ADC (perilesional) value was found in RNMO cases 1.39×10-3mm^2/sec and lowest ADC value was found in the case of PPMS 1.0×10-3mm^2/sec. The mean ADC value of all case at perilesional of lesion was 1.16×10-3mm^2/sec (SD= 0.1×10-3mm^2/sec).

Highest mean ADC value (NAWM) was found in the case of PPMS (1.12×10-3mm^2/sec) and lowest value was found in case of PML associated with HIV encephalopathy (0.95×10-3mm^2/sec).

DISCUSSION

DTI in demyelinating diseases

Diffusion imaging is based on the measurements of motion of water molecules in the tissue.[7] Pathological processes that alter the normal brain structure may affect motion and diffusion of water molecules, with effects on the diffusion indices. Diffusion images can be acquired from a minimum of three gradient directions, which yield two different kinds of sequence: diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI), respectively.[8] The diffusion tensor is a matrix acquired from at least 6 gradient directions and shows three dimensional water movement. The DTI metrics used most, derived from a mathematical combination of three eigenvectors, are Apparent diffusion coefficient (ADC) which measures overall water motion without any directionality, and fractional anisotropy (FA), which reflects the prevalence of diffusivity along a direction. ADC is quantitative metric of water diffusion, higher the ADC value higher the diffusivity. FA is a scalar value ranges from 0 to 1that is highest in compact white matter tracts, decreases in gray matter and approaches to 0 in the CSF.[9] ADC and FA have more recently been shown to be affected mainly by myelin content and to lesser extent, by axonal density.[10,11] FA is believed to be more sensitive to detection of integrity of white matter.[12,13]

Diffusion tensor imaging in multiple sclerosis

We found mean FA of core lesion was 0.307±0.06, mean FA of perilesional region was 0.444±0.03 and mean FA of NAWM was 0.567±0.06. The mean FA value obtained from white matter of control group was 0.712±0.03. Guo et al found in their study of DTI evaluation of normal appearing white matter in Multiple Sclerosis patients, mean FA values of core of lesion 0.280, perilesional region 0.383 and NAWM 0.493.[14] Temel et al found mean FA of core 0.400, perilesional region 0.460 and NAWM 0.465.[15] Tievsky et al in their study of DTI evaluation of acute and chronic lesions of Multiple

Sclerosis, found that the mean FA of core of lesion was 0.400.[16] Bammer et al in their study of DTI in characterizing diffuse and focal white matter lesion in Multiple Sclerosis patients, found that mean FA of core was 0.440.[17] Werring et al found that mean FA of core was 0.540.[13] The FA values in our study were closest to those obtained in the study by Temel et al.

Comparison of mean ADC values in MS patients

In our study we found the mean ADC of core of lesion to be 1.27×10-3mm^2/sec±0.39×10-3mm^2/sec, perilesional region 1.18×10-3mm^2/sec±0.10×10-3mm^2/sec and NAWM 1.07×10-3mm^2/sec±0.47×10-3mm^2/sec. ADC values obtained from white matter of control group was 1.02×10-3mm^2/sec±0.39×10-3mm^2/sec. Guo et al in their study of DTI evaluation of normal appearing white matter in Multiple Sclerosis patients found mean ADC of core 1.02×10-3mm^2/sec, perilesional region 0.78×10-3mm^2/sec and NAWM 0.72×10-3mm^2/sec. Temel at al in their study of DTI in patients of Multiple Sclerosis found mean ADC of core 1.08×10-3mm^2/sec, perilesional region 0.91×10-3mm^2/sec and NAWM 0.85×10-3mm^2/sec. The results of ADC value in our study were similar to those found in other studies of Diffusion tensor imaging in Demyelinating lesions. The ADC values in our study were slightly higher at all 3 regions in each patient as compared to values in these regions in aforesaid studies.

The apparent extension of the demyelination process in Multiple sclerosis beyond the borders of plaques that appear well marginated on T2-weighted images. The reasons for the apparent extension of the disease process in Multiple Sclerosis beyond the borders of visible plaques are not yet clear. It has been hypothesized that the decreased N-acetylaspartate level and N-acetylaspartate-to-creatine ratio seen in white matter regions outside of plaques at MR spectroscopy may be due to wallerian degeneration.[18] An alternative explanation for the presence of axonal injury and demyelination adjacent to plaques is suggested by their natural history of evolution. During their evolution, MS plaques enlarge and regress in a concentric manner around a perivenular focus.[19] This pattern of expansion and regression occurs in both acute and reactivated chronic plaques.[19] As plaques regress, they may leave behind a surrounding area of damaged white matter that appears to have normal signal intensity at T2-weighted MR imaging. Myelin breakdown products and transected axons have been found at the periphery of both active and reactivated chronic plaques at histologic analyses.[19-21]

We found a moderately inverse correlation between FA and ADC values obtained from core, perilesional and NAWM region. (pearson co-efficient r = -0.54). Guo et al also found a strong inverse correlation between the FA and ADC values (pearson co-efficient r= -0.9).[14] The close inverse correlation between decreased anisotropy and increased ADC suggests that the disease processes in MS result in an overall increase in water diffusivity (ADC), as well as a decrease in diffusion anisotropy (FA), probably as a result of a breakdown of diffusion barriers.[14]

Among different phenotype of Multiple Sclerosis, we found the mean FA value at lesion core in patients of CIS was 0.336, in patients of RRMS FA value at lesion core was 0.289 (Figure 1), in patients of SPMS was 0.326, in patients of PPMS it was 0.277. The mean FA of NAWM on the other hand in patients of CIS was 0.541, in case of RRMS was 0.667, in case of SPMS was 0.537, in case of PPMS was 0.497. The mean FA value at core of demyelinating plaque was found lesser in RRMS patients (0.289) than in SPMS patient (0.326) in our study. However, FA of NAWM showed lower value in case of SPMS patient (0.537) than in RRMS patients (0.667), this may be due to widespread microstructural abnormality in bilateral white matter.

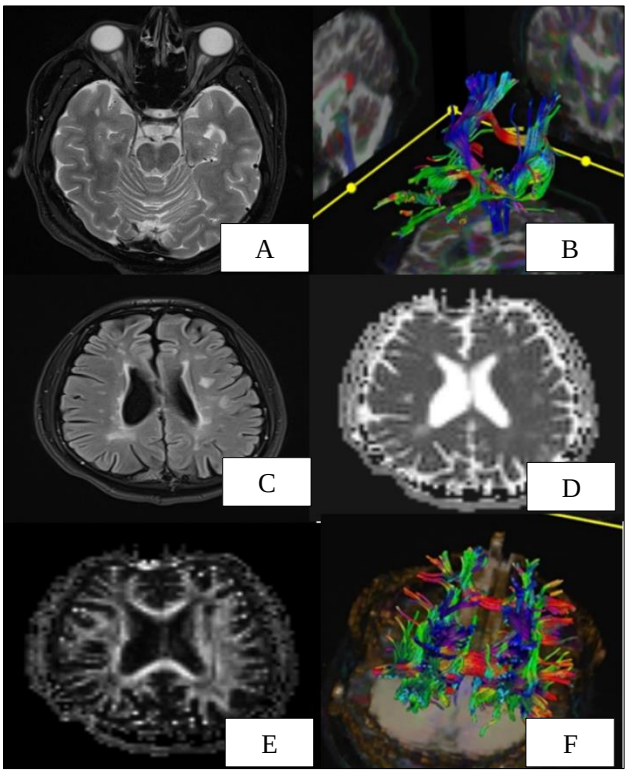

Figure 1: RRMS. Axial T2w fat sat image of brain (A) atrophic changes in bilateral optic nerve (orange arrow), 3D tractography image (B) loss of left sided optic nerve fibers (yellow arrow). Axial FLAIR image (C) hyperintense demyelinating plaques (yellow circle) in bilateral periventricular region. Lesions appear bright on ADC map, red circle (D) and dark on FA map, green circle (E) 3D Tractography image (F) fibre loss (blue solid arrow) in bilateral white matter tracts.

Bozzali et al found that DTI measurements of NAWM significantly differed in patients of SPMS and RRMS, anisotropy changes were more evident in NAWM of

SPMS patients than in RRMS patients.[22] We also found a significantly lower FA value in NAWM of SPMS in comparison with RRMS ($p<0.05$).

Out of total 30 patients 11 patients showed Gadolinium enhancement. Out of these 11 patients with enhancing lesions 8 cases were of Multiple Sclerosis. Therefore, 61.5% of patients with multiple Sclerosis in the present study showed enhancement on post contrast study. Mean FA and ADC of enhancing lesions were found to be 0.214 and 1.37×10-3mm^2/sec respectively; and non enhancing lesions were found to be 0.293 and 1.28×10-3mm^2/sec. In our study, enhancing lesions had lower FA and higher ADC values as compared to non enhancing lesions. Werring et al, Castriota et al in their study of application of DTI in Multiple Sclerosis patients showed similar findings.[13,23] The result of our study was similar to the FA and ADC values of enhancing lesions in demyelinating plaques in Multiple Sclerosis in the study conducted by Filippi et al.[24] Bammer et al concluded that FA was markedly reduced in enhancing portion of lesions suggesting pronounced ongoing tissue destruction of the white matter microstructure at the site of enhancement.[17]

NMO

Amongst all cases in sample population highest mean ADC of core was obtained in Relapsing NMO patients (1.55×10-3mm^2/sec). In our sample population all of these patients had lesions involving long segment of cervical spine. In our study, in these patients of NMO, we did not find a single intracerebral lesion. We did not get lesions in optic nerve in any of the 4 patients of RNMO. We calculated diffusion indices from spinal lesions, Mean FA value of core and NAWM were 0.342 and 0.599. Qian et al concluded that there was significant difference in FA values of NAWM in spine in case and control group.[25] We found mean FA value of white matter of control group was 0.712 which was significantly higher ($p<0.01$).

ADEM

There was gradual increase noted in mean FA values from core (0.247) to perilesional region (0.423) to NAWM region (0.698) in all 3 patients of ADEM. There was decrease in corresponding ADC value from core (1.24×10-3mm^2/sec) to perilesional region (1.1×10-3mm^2/sec). However mean ADC value of NAWM (1.1×10-3mm^2/sec) is comparable with ADC value of perilesional region (Figure 2).

In ADEM, mean FA values of core, perilesional and NAWM was different significantly ($p<0.01$). Lowest anisotropy was found at core of lesion where highest degree of tissue destruction present. Also a lower FA value was obtained from perilesional region, so there was white mater microstructure abnormality surrounding lesion which was not visible on T2/FLAIR sequences. Chen C et al concluded DTI parameters can depict more microstructural change than conventional MRI in ADEM patients.[26] Chen C et al found in their study FA of core of lesion was 0.16 and ADC 0.99×10-3mm^2/sec, in our study we found mean FA of core to be 0.247 and mean ADC 1.24×10-3mm^2/sec.[26] We found higher FA and ADC values of core lesion in comparison to FA and ADC values obtained in the aforesaid study. Similarly, Balasubramanya et al found ADC of core to be 1.24×10-3mm^2/sec and NAWM 0.93×10-3mm2/sec in ADEM patients.[27] Mean ADC value obtained from core in our study is comparable with this study. Lower anisotropy values at core of lesion in ADEM patients signify more tissue destruction than MS patients, however NAWM region of MS patients revealed lower anisotropy value than NAWM of ADEM patients. So there was more white matter microstructural abnormality in NAWM of MS patients. We found discordant ADC values when comparing with FA values. One possible explanation is anisotropy values are more sensitive in detection of white matter microstructural abnormalities than diffusivity values.[14]

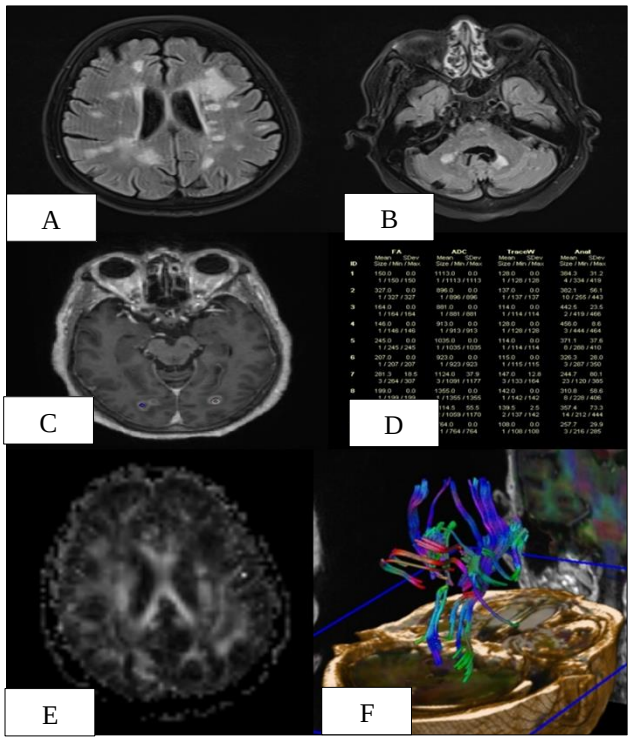

Figure 2: ADEM. Axial FLAIR image of brain (A, B) multiple hyperintense demyelinating lesions in bilateral corona radiata and cerebellar white matter (yellow arrow). (C) ROI plotted on enhancing lesion (D) FA and ADC chart. Demyelinating lesions appear dark on FA map, green circle (E) 3D tractography image (F) loss of bilateral white matter fibres (red arrow).

PML

In our study we found 5 patients out of total 30 had PML on CSF correlation. Of these 5, 1 patient was PML-IRIS

and 1 patient of PML had associated HIV encephalopathy (Figure 4). We found lowest mean FA of lesion core in patient of PML with HIV encephalopathy (0.17) and this value was also the lowest mean FA value compared to all demyelinating lesion in the entire sample population. In all 3 patients of PML, the patients of PML-IRIS and PML with HIV encephalopathy showed gradual increase in FA values from core to NAWM. For all 3 cases of PML, mean ADC failed to show the inverse relationship with mean FA values in the core and perilesional region. (Mean ADC of core 1.1×10-3mm^2/sec and mean ADC of perilesional region 1.13×10-3mm^2/sec).The lowest FA of lesion core in PML associated with HIV encephalopathy may denote that there is greater microstructural distortion due to extensive demyelination likely due to double viral load in comparison with PML or PML-IRIS. Our result are in agreement with the study conducted by Kuchelmeister et al ,which stated that there was extensive white matter damage in concomitant HIV encephalopathy in PML patients.[28]

SACD

In our study 4 patients out of 30 had demyelinating lesions due to nutritional etiology. In these 4 patients of SACD on biochemical correlation Vit B12 deficiency was present in 3 patients while one patient had both Vit B12 and copper deficiency. All 4 cases of SACD in our study showed demyelinating lesions in spinal cord along with sparing of brain on MR. On MRI there was long segment involvement of dorsal and lateral cord in all 4 patients. In all 4 patients DTI demonstrated gradual increase in FA values from core (0.326) to NAWM (0.509). The mean FA value of core in 3 patients with Vit B12 deficiency was found to be 0.341 and the mean FA of core in patient with Vit B12 and copper deficiency was 0.311. The mean FA of NAWM (0.483) in patient with Vit B12 and copper deficiency was lower than the mean FA of NAWM (0.536). We also found that in the patients of Vit B12 deficiency induced SACD the mean ADC of perilesional region (1.17×10-3mm^2/sec) was higher than the mean ADC of core(1.15×10-3mm^2/sec). The lower anisotropy values in core and normally appearing white matter in patient with combined Vit B12 and copper deficiency denotes that there was more severe white matter microstructure damage in the lesion core and NAWM likely due to dual deficiency. The reason for higher ADC values in perilesional region is anisotropy values are more sensitive to detect white matter microstructural involvement than diffusivity parameters, however we could not compare with any previous literature in SACD.

Wernicke's encephalopathy

In the present study, out of 30 patients one patient was categorized as Wernicke's encephalopathy on clinic-radiological correlation. This patient was found to have low thiamine on biochemical analysis. In this patient demyelinating lesions were seen in mamillary bodies on MR. Mean FA of core was 0.274, perilesional region 0.520 and NAWM 0.579 and mean ADC value of core was 1.24×10-3mm^2/sec, perilesional region 1.11×10-3mm^2/sec and NAWM 1.10×10-3mm^2/sec. There was progressive increase in FA and corresponding decrease in ADC values from lesion core to perilesional region to NAWM. This is similar to the FA and ADC values in all demyelinating lesions in our study except for ADEM, PML and SACD cases. However in literature we have not come across any case of nutritional Wernicke's encephalopathy due to thiamine deficiency.

DTI Tractography

The objective of DTI fibre tracking is to determine intervoxel connectivity on the basis of the anisotropic diffusion of water.[29,30] In each brain voxel, the dominant direction of axonal tracts can be assumed to be parallel to the primary eigenvector of the diffusion tensor. Fibre tracking uses the diffusion tensor of each voxel to follow an axonal tract in 3D from voxel to voxel through the human brain. Because DTI provides only microstructural information at relatively low spatial resolution, DTI fibre tracking is often combined with functional and/or higher resolution anatomic information to delineate specific pathways.[31] In this way, 3D DTI tractography has opened up a whole new dimension to the ability to depict human neuroanatomy noninvasively. 3D tractography permits reconstruction of large fibre bundles using 3Dt Tractography.[32] After the selection of one or more than one, region of interest, nerve pathways are reconstructed by tracking along the principal direction of fibre passing through region of interest. This technique can be used to analyse displacement of fibres as well as to detect wallerian degeneration.

Out of total 30 patients in our study, disruption of white matter fibre tracts was detected in 20 patients with demyelinating lesions while in 10 patients no disruption of tracts was detected. Thus in 66.6% of total sample population, disruption of white matter fibre tracts was found and in 33.3% cases no white matter tracts disruption was noted on diffusion tractography. Out of these 20 patients we found 14 patients (70% of the total number of patients with fibre loss and 46.6% of total study population) with significant fibre loss. Out of 14 patients with significant fibre loss, 8 patients were of MS (26.6% of total study population), 2 patients had ADEM (6.6%), 1 patient had NMO (3.3%), 1 patient was of PML-IRIS (3.3%), 1 patient was of PML associated with HIV encephalopathy (3.3%) and 1 patient was of SACD (3.3%). Amongst Multiple Sclerosis patients in our study, phenotypes associated with significant loss of fibre were RRMS, SPMS and CIS. In one patient we found loss of white matter tracts of left corticospinal tract on 3D tractography. This patient was of RRMS phenotype with prior 7 episodes of relapse and prolonged duration of disease (20 years). DTI tractography demonstrated paucity of left optic nerve fibres in one patient (Figure 1).

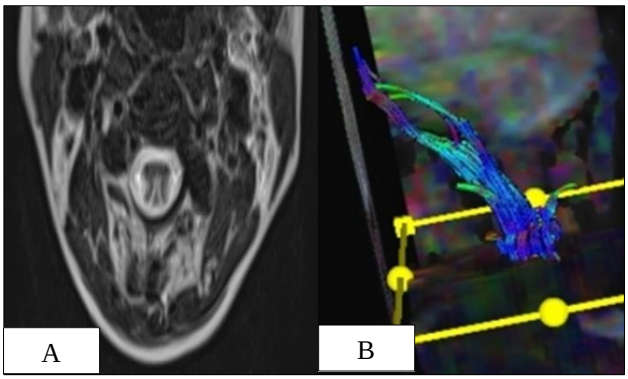

Figure 3: SACD. T2w axial image (A) hyperintensity in posterior (green arrow) and lateral column of cord (yellow arrow). 3D tractography image (B) paucity of posterior column white matter tracts (red arrow).

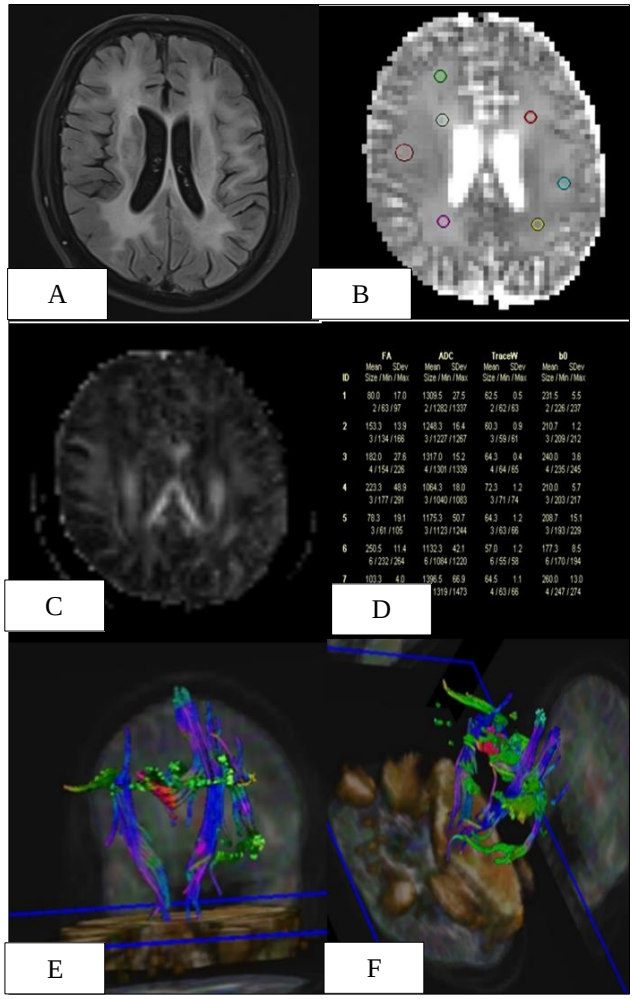

Figure 4: PML associated with HIV encephalopathy. Axial FLAIR (A) image of brain showing bilateral extensive white matter involvement with involvement of subcortical U fibres. Lesions appear dark on FA map (B) and bright on ADC map (C). (D) FA and ADC chart. 3D tractography images (E,F) white matter fibre loss in bilateral corticospinal tract (right > left).

Clinically the patient had dimness of vision in bilateral eyes and belong to RRMS phenotype. On DTI Tractography significant loss of white matter tracts in bilateral cerebral hemisphere was found in one patient of Secondary Progressive Multiple Sclerosis. In this patient of SPMS, T2 MR showed a very high lesion load. In a single patient of PPMS phenotype, on DT Tractography we could not find significant white matter loss and this was a deviation in spite of progressive nature of the disease. In one patient of NMO and one patient of SACD, DT Tractography demonstrated thinning of white matter tracts in dorsal and lateral column (Figure 3).

CONCLUSION

DTI is a useful MR technique that allows quantification of extent of demyelination in the white matter. Quantification of white matter microstructural derangement and myelin loss in demyelinating diseases of CNS evaluation of two parameters; the Fractional Anisotropy (FA) and the Apparent Diffusion Coefficient (ADC). The FA values obtained by DTI depend on anisotropy and are linked with directionality and therefore are more reliable marker of demyelination compared to ADC values which are independent of directionality and therefore less reliable. In our study DTI demonstrated a strong inverse correlation between FA and ADC values obtained from core, perilesional region in primary as well as secondary demyelinating disease (pearson co-efficient r=-0.71).This inverse correlation is an indicator of decreased diffusion anisotropy and as well as increased water diffusivity as a result of breakdown of diffusion barriers associated with demyelination. DTI in NAWM in demyelinating diseases helps to identify the extent of demyelination by demonstrating lower FA values in NAWM. DTI is better than T2 MR and CEMR because it can identify presence of white matter microstructural damage in white matter regions remote from lesion. Lower anisotropy values at core of lesion in ADEM patients signify more tissue destruction than MS patients. Thus, DTI throws more light on the pathophysiology and microstructural changes of demyelination. DTI Tractography is very useful in demonstrating disruption of white matter tracts. The greater the lesion load greater the disruption in white matter fibre tracts and there is direct correlation between extent of tract disruption, lesion load and clinical symptomatology at presentation. DTI Tractography finding may play a role in management of patients of demyelinating disease; the clinicians can follow a more aggressive and proactive therapeutic protocol in patients who demonstrated greater white matter disruption on Tractography.

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