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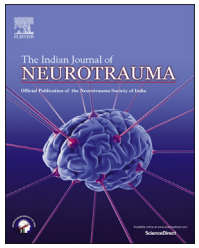

Original Article

# Can diffusion tensor imaging predict outcome in acute traumatic deterioration of degenerative cervical spine disease

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ABSTRACT

*Introduction:* Patients with degenerative diseases of cervical spine are likely to develop acute cord injury following trivial trauma. However many of them can have a poor functional outcome. Routine MRI may not be helpful in accurately predicting the recovery in these cases. DTI of spinal cord is a promising tool in prognostication of various neurological diseases.

*Materials and method:* A prospective study was done to know the use of DTI in predicting outcome in acute deterioration of degenerative cervical spine disease. Cases presenting within 48 h of acute traumatic deterioration were included in the study. A screening MRI was done to know the extent of disease and cord damage. Using DTI, apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were calculated at the level of injury. 3D tractography was done using Label map seeding technique. Clinical correlation was done with ASIA and FIM scores.

*Results:* Five cases of cervical cord injury with a mean age of 46 ± 11 years were studied. The diffusion parameters were compared with three age matched controls. The cases were followed up prospectively. All the cases had a decrease in ADC values and increase in FA at the level of injury compared to other levels ( $p = 0.02$) and to normal controls ( $p = 0.001$). It was extending beyond the level of cord contusion identified by routine MRI.

*Discussion:* DTI is well suited for evaluating effects of spinal cord injury like cellular swelling and myelin membrane disruption which is not diagnosed using conventional MRI. ADC helps us to define the type and extent of spinal cord injury. 3D tractography delineates the fiber disruption.

*Conclusion:* ADC is a sensitive marker of acute cervical cord injury, in degenerative spine disease.3D tractography can help us to select the cases for early surgical intervention and to predict clinical outcome.



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## 1. Introduction

Patients with degenerative cervical spine disease can deteriorate following a trivial trauma. These patients are often quadriplegic and have profound functional disability. Recovery from spinal cord injury is clinically unpredictable in the acute stage but is important in the functional rehabilitation point of view. Although the anatomical features are well visualized with conventional MRI, the integrity of white matter tracts within the spinal cord is not well evaluated. Subsequently, there has been only limited success in utilizing MRI as a prognostic tool at time of injury because the degree of white matter injury primarily determines the functional ability of patients.[1]

Diffusion-weighted MRI (DWI) has been proposed as a method to evaluate the integrity of white matter tracts in the spinal cord.[2] Diffusion tensor imaging (DTI) is a novel MRI technique that can provide information about the microscopic tissue architecture.[3] DWI can provide numerical data; however, the current experimental and clinical research is unclear as to how these data should be obtained, measured, and analyzed. There are many possible diffusion parameters that may be derived from DWI data, including simple apparent diffusion coefficients (ADCs), tensors derived from diffusion tensor imaging (DTI), and multiple methods for characterizing directional variations in diffusion properties. Fractional anisotropy (FA) is a convenient measure scaled from 0 (complete isotropic diffusion) to 1 (complete anisotropic diffusion) used to characterize the local coherence of fibers.[4] In white matter, water diffusion is less restricted in the direction parallel to the fiber orientation.

There are many experimental studies that have proven that DWI of the spinal cord may be a powerful method of detecting structural damage to the spinal cord as compared to conventional MRI. Questions still remain as to exactly what the data mean and how they should be interpreted. Further work delineating the histological correlates to the ADC values and anisotropy measures is required.[5] By developing a normal DTI atlas, numerous potential clinical applications in which one may quantify the degree of micro structural impairment within the spinal cord could be identified.[6] DTI parameter abnormalities were greatest at the cord injury site and reflected severity of injury.[7] A recent study demonstrate for the first time that axial diffusivity (lambda||), derived from diffusion tensor imaging (DTI) within 3 h after SCI, accurately predicts long-term locomotor behavioral recovery in mice[8].

There are only a few international studies that have reported the ability of DTI to predict long term recovery following cervical spine injury in humans.[4,7,9] Hence, a study was undertaken to look for correlation between the DTI parameters and the clinical severity in acute post traumatic deterioration of degenerative cervical spine disease.

## 2. Methods

A pilot study was done in our institute in cases of acute traumatic deterioration of degenerative cervical spine disease from January 2010 to January 2012. The patients who had presented within 48 h of spinal cord injury were screened with routine MRI of cervical spine to identify the cord injury and pre-existing degenerative spine disease. After obtaining an informed consent, the patients who were hemodynamically stable and conscious underwent DTI of the cervical cord. Patients with head injury, polytrauma and other neurological or systemic disease that may affect neurological function were excluded. ASIA and FIM scores were measured as per the standard protocol.

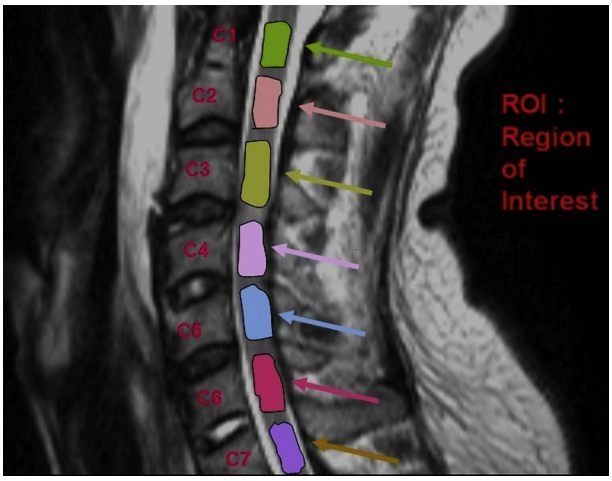


**Fig. 1 – Selection of ROI for multi-voxel measurement of diffusion coefficients at each cervical level.**

Imaging was performed using axial, multi–shot, echo-planar parallel DT imaging with an acceleration factor of two, 16 non collinear gradient directions with two b values (b: 0 and 1000 s/mm$^2$). Following the distortion correction, the mean ADC and FA was calculated at each level of the spinal cord from C1 to C7 using the method described below. b:0 images were utilized for this as they permitted clear visualization of the lesions. Mid sagittal images were used in the selection of each region-of-interest (ROI) to avoid

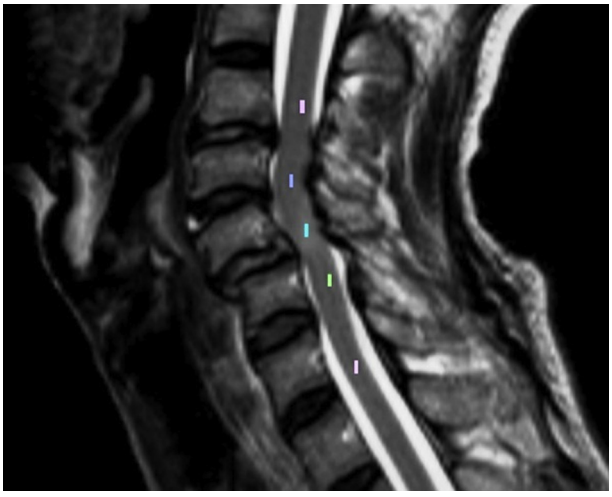

**Fig. 2 – Single voxel based ADC and FA values measurement.**

**Table 1 – Clinical features, management and follow up.**

| Pt. | Age sex | Mode of injury | MRI finding of pre-existing degenerative disease | 3DTractography | Management | Initial | | Follow up | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ASIA (100) | FIM (91) | Months | ASIA | FIM |
| 1 | 50 M | Seizure and fall | Disc-osteophyte at C3–4 | Disrupted | Conservative | 30 | 13 | 24 | 58 | 87 |
| 2 | 35 F | Fall from own height | Disc-osteophyte at C4–5, C5–6 & C6–7 | Displaced | C6 corpectomy & fusion | 80 | 51 | 8 | 100 | 91 |
| 3 | 60 F | Slip and fall | OPLL C3 to D1 | Absent | Conservative | 21 | 13 | 7 | Expired | |
| 4 | 35 M | Fall from tree | Disc-osteophyte at C3–4 | Disrupted | Conservative | 44 | 13 | 5.5 | Expired | |
| 5 | 50 M | RTA - pillion | Disc-osteophyte C4–5, C5–6 Subluxation (Gr.1) | Displaced | C56 fusion | 78 | 38 | 20 | 100 | 91 |

cerebrospinal fluid partial volume effects, magnetic susceptibility and motion artefacts.[6] ROI was carefully marked manually by including the maximum substance of cord (voxels) behind each vertebral body and excluding the CSF signal.[7] Selection of region-of-interest (ROI) is demonstrated in Fig. 1. From these, the ROIs were copied to the FA maps. We applied the whole cord analysis, including both the white and gray matter but excluding the regions of cord corresponding to disc levels. The separation of the gray and white matter was not attempted due to challenges of image resolution in sagittal sections. The regions-of-interest were delineated to exclude approximately one voxel from the edge of the cord along the anterior and posterior margins. Using this technique, trimming of ROI was minimized and bulk of the white matter that was located at the periphery of the cord was included. Mean (multi voxel) ADC and FA were obtained at each level. Single voxel based ADC and FA values were measured at each cervical segment. ADC and FA were measured at the level of cord contusion and two levels proximally and distally (Fig. 2). 3D tractography was done using Label map seeding technique.[10–12] Three-dimensional fiber tracts were created using the principal diffusion directions method, for which the eigenvector corresponding to the largest eigenvalue is extracted from the diffusion tensor field generated from the DTI datasets in the region where diffusion was linear.[10] The number of fiber projections is the number of reconstructed streamlines that penetrated the region-of-interest (ROI). This parameter has to be interpreted as a relative parameter and is not a measure of the true number of axons passing through the ROI. However the white matter tracts were not clustered into groups as the volume of the cord available for fiber tracting without CSF artifact is very less. Secondly, cervical cord injury usually involves the whole of the white matter fibers at the level of injury, unlike diseases like multiple sclerosis where calculation of fractional anisotropy of individual tracts in a cross section can be useful and are published.[13,14] Even in experimental studies of hyper acute spinal cord injury, quantitative relative anisotropy map measurements identified only the presence or absence of moderate-to-severe SCI despite superior gray-white matter contrast. Significant distinction between the two injury grades with respect to white matter was not found. Decreased axial diffusivity and radial diffusivity greatly impaired the ability of RA to detect white matter injury in this report.[15]

**Table 2 – Mean DTI values of normal controls at each level.**

| Level | Multi voxel | |
|---|---|---|
| | ADC | FA |
| C1 | 2.45 | 0.31 |
| C2 | 2.32 | 0.36 |
| C3 | 1.76 | 0.57 |
| C4 | 1.47 | 0.61 |
| C5 | 1.49 | 0.55 |
| C6 | 1.68 | 0.48 |
| C7 | 1.63 | 0.52 |
| Whole cord | 1.76 | 0.52 |

**Table 3 – Mean multi voxel and point voxel coefficients of case 1.**

| Level | Voxels | Multi voxels mean ADC | Multi voxels mean FA | Point voxel measurements | ADC | FA |
|---|---|---|---|---|---|---|
| C1 | 54 | 1.32 ± 0.78 | 0.76 ± 0.19 | Site of injury 1 | 0.74 | 0.88 |
| C2 | 40 | 1.07 ± 0.45 | 0.80 ± 0.16 | Site of injury 2 | 0.66 | 0.87 |
| C3 | 73 | 0.88 ± 0.36 | 0.84 ± 0.12 | Site of injury 3 | 0.90 | 0.82 |
| C4 | 68 | 0.89 ± 0.24 | 0.82 ± 0.08 | 1 level above | 0.62 | 0.94 |
| C5 | 55 | 0.89 ± 0.22 | 0.85 ± 0.07 | 2 level above | 0.60 | 0.91 |
| C6 | 45 | 0.95 ± 0.33 | 0.76 ± 0.20 | 1 level below | 0.85 | 0.93 |
| C7 | 53 | 1.25 ± 0.55 | 0.63 ± 0.25 | 2 level below | 1.02 | 0.86 |

**Table 4 – Mean multi voxel and point voxel coefficients of case 2.**

| Level | Voxels | Multi voxels mean ADC | Multi voxels mean FA | Point voxel measurements | ADC | FA |
|---|---|---|---|---|---|---|
| C1 | Could not be measured | | | Site of injury 1 | 0.77 | 0.82 |
| C2 | 46 | 1.14 ± 0.45 | 0.75 ± 0.13 | Site of injury 2 | 0.82 | 0.85 |
| C3 | 80 | 1.16 ± 0.21 | 0.71 ± 0.16 | Site of injury 3 | 0.75 | 0.80 |
| C4 | 78 | 0.97 ± 0.14 | 0.72 ± 0.13 | 1 level above | 0.95 | 0.86 |
| C5 | 69 | 0.89 ± 0.10 | 0.78 ± 0.12 | 2 level above | 1.02 | 0.77 |
| C6 | 55 | 0.93 ± 0.14 | 0.76 ± 0.16 | 1 level below | 0.93 | 0.95 |
| C7 | 47 | 1.08 ± 0.39 | 0.76 ± 0.17 | 2 level below | 1.84 | 0.80 |

**Table 5 – Mean multi voxel and point voxel coefficients of case 3.**

| Level | Voxels | Multi voxels mean ADC | Multi voxels mean FA | Point voxel measurements | ADC | FA |
|---|---|---|---|---|---|---|
| C1 | Could not be measured | | | Site of injury 1 | 0.48 | 0.9 |
| C2 | 27 | 0.21 ± 0.20 | 0.72 ± 0.32 | Site of injury 2 | 0.22 | 0.8 |
| C3 | 43 | 0.23 ± 0.21 | 0.81 ± 0.24 | Site of injury 3 | 0.21 | 1.0 |
| C4 | 36 | 0.22 ± 0.21 | 0.80 ± 0.30 | 1 level above | 0.32 | 0.83 |
| C5 | 25 | 0.40 ± 0.29 | 0.80 ± 0.25 | 2 level above | 0.22 | 0.99 |
| C6 | 36 | 0.26 ± 0.20 | 0.83 ± 0.12 | 1 level below | 0.62 | 0.87 |
| C7 | 49 | 0.60 ± 0.32 | 0.71 ± 0.22 | 2 level below | 0.42 | 0.77 |

Three age matched ($p = 0.786$) controls with normal MRI were included in our study for comparison. The multi voxel and single voxel ADC and FA were calculated for these controls similarly.

Further; the patients underwent surgical management according to the clinical indication. The treating surgical team was blinded to the DTI parameters. This was followed by physiotherapy and rehabilitation as per the institute clinical protocol. The cases were followed up. The ASIA and FIM scores were calculated at follow up. The investigator who analyzed the DTI data was blinded to the study and outcome.

**Table 6 – Mean multi voxel and point voxel coefficients of case 4.**

| Level | Voxels | Multi voxels mean ADC | Multi voxels mean FA | Point voxel measurements | ADC | FA |
|---|---|---|---|---|---|---|
| C1 | 82 | 1.93 ± 0.99 | 0.31 ± 0.19 | Site of injury 1 | 0.80 | 0.46 |
| C2 | 79 | 2.32 ± 0.83 | 0.34 ± 0.17 | Site of injury 2 | 0.93 | 0.35 |
| C3 | 77 | 1.1 ± 0.43 | 0.57 ± 0.19 | Site of injury 3 | 0.73 | 0.56 |
| C4 | 79 | 1.22 ± 0.41 | 0.57 ± 0.17 | 1 level above | 1.39 | 0.44 |
| C5 | 70 | 1.56 ± 0.42 | 0.43 ± 0.17 | 2 level above | 3.45 | 0.25 |
| C6 | 62 | 1.87 ± 0.82 | 0.41 ± 0.18 | 1 level below | 1.09 | 0.80 |
| C7 | 56 | 1.35 ± 0.76 | 0.46 ± 0.21 | 2 level below | 1.04 | 0.38 |

**Table 7 – Mean multi voxel and point voxel coefficients of case 5.**

| Level | Voxels | Multi voxels mean ADC | Multi voxels mean FA | Point voxel measurements | ADC | FA |
|---|---|---|---|---|---|---|
| C1 | Could not be measured | | | Site of injury 1 | 0.80 | 0.73 |
| C2 | 30 | 1.52 ± 0.84 | 0.63 ± 0.17 | Site of injury 2 | 0.82 | 0.78 |
| C3 | 55 | 1.12 ± 0.42 | 0.69 ± 0.11 | Site of injury 3 | 0.83 | 0.64 |
| C4 | 50 | 0.49 ± 0.17 | 0.72 ± 0.08 | 1 level above | 1.06 | 0.71 |
| C5 | 44 | 1.06 ± 0.19 | 0.60 ± 0.10 | 2 level above | 0.91 | 0.82 |
| C6 | 50 | 1.31 ± 0.51 | 0.44 ± 0.15 | 1 level below | 2.21 | 0.47 |
| C7 | 48 | 1.95 ± 0.65 | 0.35 ± 0.15 | 2 level below | 1.59 | 0.27 |

**Table 8 – Comparison of mean whole cord ADC and FA values between patients and controls.**

| Whole cord | | Mean ADC | Mean FA |
|---|---|---|---|
| Patients | 1 | 0.99 | 0.79 |
| | 2 | 1.03 | 0.75 |
| | 3 | 0.32 | 0.78 |
| | 4 | 1.57 | 0.46 |
| | 5 | 1.24 | 0.57 |
| Controls | 1 | 1.85 | 0.48 |
| | 2 | 1.75 | 0.49 |
| | 3 | 1.67 | 0.57 |

## 3. Statistical analysis

SPSS 10.0 was used for data analysis. (SPSS 10.0 program, SPSS, Inc., Chicago, IL). Normally distributed values between two variables were compared by unpaired *t* test and Mann Whitney *U* test. The percentages were compared using the $X^2$ test. $P < 0.05$ will be considered significant.

## 4. Results

There were five cases of acute traumatic deterioration in pre-existing degenerative cervical spine disease (Table 1). Four patients had cervical spondylosis and one had OPLL. Though the cases were not symptomatic before the trauma, all were quadriparetic following trauma with bladder involvement in one case. The mean (multi voxel) ADC and FA of the controls were measured (Table 2). There was a downward trend in all the diffusivities toward the lower cervical cord.

In all the cases, multi voxel DTI parameters at each cervical segment and point voxel DTI parameters at the level of injury and two segments above and below it were measured (Tables 3–7).The cases were followed up for a mean period of 12.9 ± 0.69 months. Two cases expired at five and seven months post trauma. Two cases had a full recovery of ASIA motor and FIM motor scores. One patient had a partial recovery.

### 4.1. *Analysis of data*

Mean whole cord ADC values of the patients were significantly reduced when compared to controls ( $p = 0.025$) *Mann Whitney U test* (Table 8).[7] There was no significant difference between point voxel ADC and FA values at the level of injury (hyper in T2WI) when compared with two levels above and below. ( $p = 0.276$ and $p = 0.358$) (Tables 3–7). This proves that the signal changes in MRI T2 weighted image do not exactly demonstrate the extent of injury. The mean ADC at the level of cord contusion (ROI based at the segments involved in contusion) was found to be significantly less compared to the controls ($P = 0.001$) and when compared to the distant areas in the same patient ( $p = 0.02$) (Table 9). However, the values were not normalizing at the radiological limit of cord contusion demonstrated in T2 weighted image again proving that the tissue damage may extend beyond that.[4]

Apparent diffusion coefficients (ADC), was found to correlate with the site of injury statistically when compared to the distant normal cord of each patient as well as to the mean diffusivity of the control population. Fractional anisotropy was not found to be significantly altered at the site or injury or

**Table 9 – Comparison of multi voxel DTI parameters (ADC and FA) at the level of injury, with control population at same level and distant normal segment of the same patient.**

| Case | Level of cord injury | ROI based: Segment of injury (mean) | | ROI based: Control at same level (mean) | | ROI based: Distant normal segment (mean) | | |
|---|---|---|---|---|---|---|---|---|
| | | ADC | FA | ADC | FA | Level | ADC | FA |
| 1 | C3 | 0.88 | 0.85 | 1.76 | 0.55 | C7 | 1.25 | 0.63 |
| 2 | C5 | 0.89 | 0.78 | 1.49 | 0.55 | C2 | 1.16 | 0.71 |
| 3 | C4 | 0.22 | 0.80 | 1.47 | 0.57 | C7 | 0.60 | 0.71 |
| 4 | C3 | 1.1 | 0.57 | 1.76 | 0.57 | C6 | 1.87 | 0.41 |
| 5 | C4 | 0.49 | 0.72 | 1.47 | 0.61 | C7 | 1.95 | 0.35 |

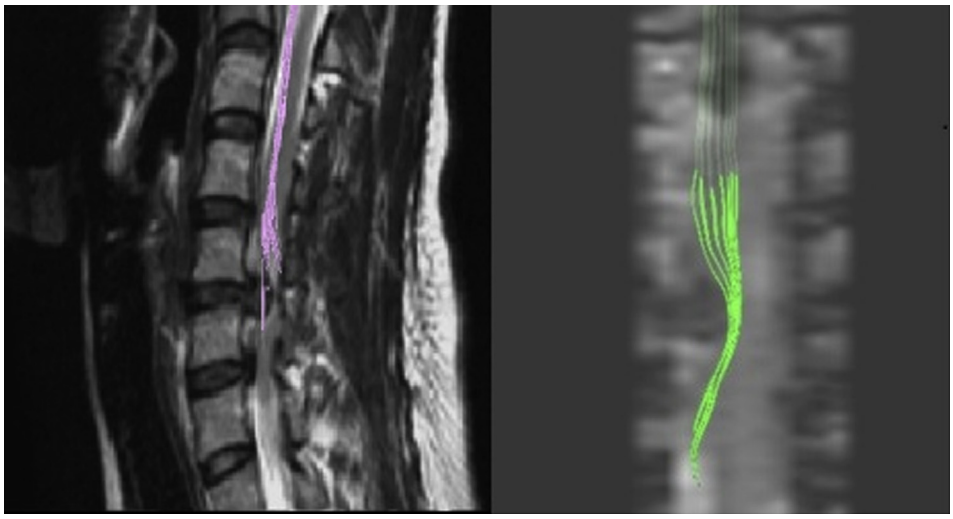

**Fig. 3 – Sagittal section shows apparent disruption at level of compression but coronal image demonstrate that only tract displacement is present (case2).**

when compared to controls. This may be due to the presence of myelin edema and bleed. ADC was the most sensitive marker of cord injury.

3D Tractography and fiber tracking of the site of injury, was found to be more accurate to predict the outcome.[9,12] In cases 2 and 5, where only displacement of fibers was seen due to the compressive lesion, near normal recovery was observed on long term follow up (Figs. 3 and 4). In case 1, a patient with minor disruption of the fibers the motor and functional recovery was partial (Fig. 5). However, in cases 3 and 4, there was total disarray of fibers with absence of tracking (Figs. 6 and 7). This was found to correlate to poor ASIA motor scores. The outcome was also dismal, as both the patients expired.

## 5. Discussion

Changes in diffusion parameters are sensitive and correlate well with the severity of spinal cord injury even in the acute stage. DTI of spinal cord will help us to predict the outcome following spine trauma as the recovery depends on the degree of fiber disarray within the cord, which in fact is studied using this. Thus DTI can help in accurate identification of site of injury by demonstrating the fiber disruption within the cord and measurement of diffusion values and anisotropy at this site. Application of these parameters can help to correlate with the severity of injury and clinical recovery.[16] This can make DTI an indispensable non-invasive tool for evaluating the axonal disruption after spinal cord injury.

Results of this study will shed some light in the utility of DTI in predicting outcome following acute spinal cord injury. With the calculation of mean axial diffusivity or fractional

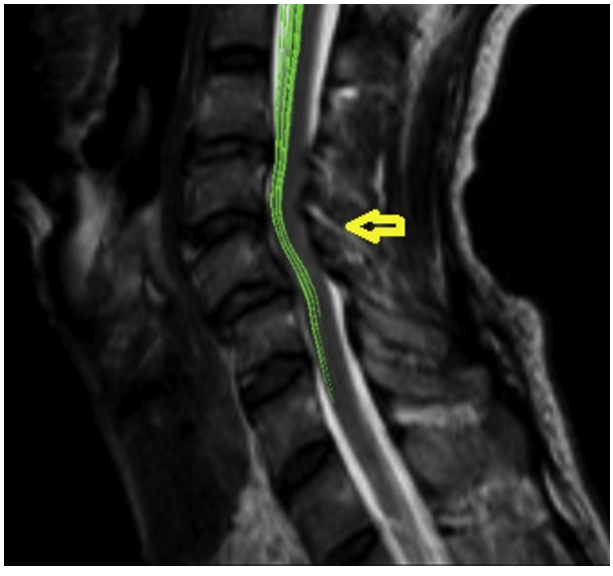

**Fig. 4 – C56 subluxation. Tractography demonstrates that there is only displacement of tracts at C45 level (case 5).**

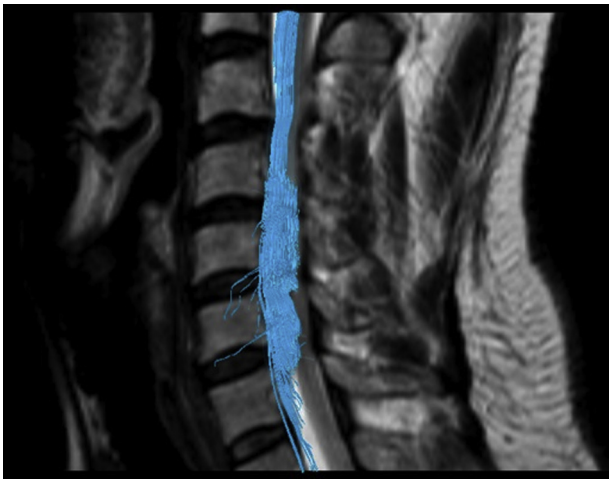

**Fig. 5 – White matter fiber tracking is poorly demonstrated at C34 level (case1).**

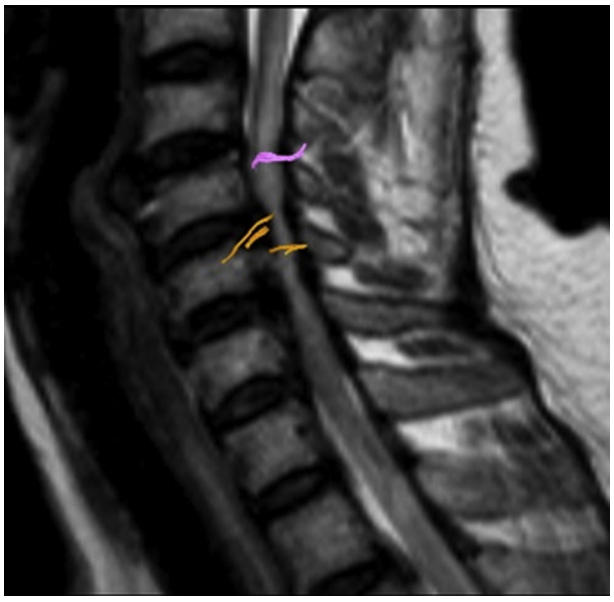

**Fig. 6 – Tractography cannot be obtained due to loss of anisotropy suggestive of white fiber disruption (case3).**

anisotropy and by drawing a tractography,[17] if we can identify the cases that are likely to have a good recovery, the treatment and rehabilitation can be more focused.[18] This can also avoid unnecessary surgery in at least some patients. This will also help in a better utilization of the available resources of rehabilitation in a developing country like ours. The ability of DTI to prognosticate cases of cervical spine injury is being demonstrated in many recent studies.[19,20] However larger studies are required before wider clinical application.

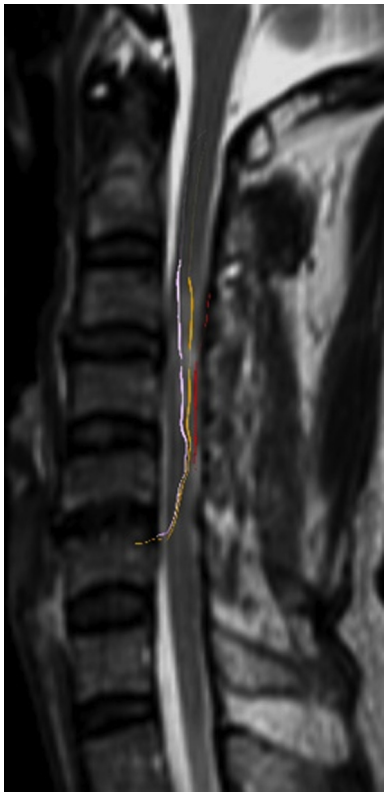

**Fig. 7 – 'Disruption' of fibers seen at level of injury (case 4).**

## Conflicts of interest

All authors have none to declare.

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