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Could MR Diffusion Tensor Imaging Help to Solve Clinical-Radiological Mismatch in Cervical Spondylotic Myelopathy?

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Abstract

Background: Cervical spondylotic myelopathy (CSM) is a major cause of motor dysfunction. The radiological diagnosis of CSM has to be made as early as possible, since surgical interference in earlier stages during the disease course was reported to be more successful and associated with favorable post-operative clinical outcome when compared with later stages. Diffusion tensor imaging (DTI) is a promising technique that could help to detect early structural cord changes in patients presenting with cervical compressive myelopathy.

Aim of Study: To investigate the utility of MR diffusion tensor imaging using its quantitative fractional anisotropy (FA) and apparent diffusion coefficient (ADC) parameters as an early detector biomarker of microstructural cord affection in cervical spondylotic myelopathy (CSM) patients with no detectable intramedullary hyperintensity in the conventional T2 WIs.

Patients and Methods: This study is a prospective study. 60 patients presented with neurological symptoms and signs of cervical compressive myelopathy with cervical spondylotic changes and normal cord signal on conventional T2 WIs were included in this study. The clinical severity of compressive myelopathy was assessed based on the mJOA score. MR diffusion tensor imaging was done for all patients. FA and ADC values of the cervical cord at level of most severe disc lesions and at non-stenotic level (C2-3, considered as internal reference) were measured and compared. The DTI parameters at level of most severe disc lesions were also correlated with disc severity score and mJOA score.

Results: At the level of most severe disc lesions; we found statistically significant reduction of FA values (mean 0.57 ±0.10 vs. 0.67±0.06 with *p*-value <0.001) and increase of ADC values (mean 1.02±0.34 vs. 0.88±0.31 with *p*-value 0.015) compared to non-stenotic reference level. FA & ADC parameters had high sensitivity for detection of early myelopathy in CSM patients with normal cord signal in conventional T2WIs (sensitivity 86.66% and 80% respectively). FA and ADC values show significant correlation with both disc severity (*p*-value <0.001 & 0.008) and clinical function mJOA score (*p*-value 0.015 & 0.031 respectively).

Conclusion: MR diffusion tensor imaging using its quantitative FA and ADC parameters is more sensitivity than conventional T2 WIs in detection of early microstructural cord affection in CSM patients and could help as an early detector biomarker of cervical myelopathy before the appearance of any detectable signal abnormalities on T2 WIs. Our study enhanced the utility of DTI in cases with CSM to solve the clinical/radiological mismatch; enabling the decision of appropriate timing of cervical decompression surgery before the chronic irreversible myelopathy changes become settled.

Key Words: *Cord compression – DTI – FA – ADC – Myelopathy.*

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Introduction

CERVICAL spondylotic myelopathy (CSM) is a major cause of motor dysfunction. Conventional magnetic resonance imaging (MRI) is the modality of choice for diagnosis of cervical spondylotic changes; yet it is known to have a low sensitivity (about 65%) in detection of cervical myelopathy. In some patients who presented with clinical symptoms of cervical compressive myelopathy, conventional MRI imaging shows no detectable cord signal abnormality. The appearance of intramedullary hyperintensity on T2 weighted images (T2 WIs) is a late sign of cervical compressive myelopathy; associated with poor prognosis and unfavorable post-operative functional outcome [1].

Diffusion tensor imaging (DTI) is a promising technique that could help to detect early structural cord changes in patients presenting with cervical compressive myelopathy which remain occult at conventional T2 WIs until late disease course. DTI may aid to improve treatment plan and surgical decision-making and thus enhancing prognosis [2].

DTI has a role to play in the pre-operative planning of patient with cervical spondylotic myelopathy; both diagnostic in detecting early cervical cord structural alterations and prognostic as evi-

dently reduced pre-operative fractional anisotropy (FA) values are associated with less favorable post-decompression surgery clinical outcome [3].

Patients and Methods

The purpose of this study was to investigate the utility of MR diffusion tensor imaging using its quantitative FA and ADC parameters as an early detector biomarker of microstructural cord changes in cervical spondylotic myelopathy (CSM) patients with no detectable intramedullary hyperintensity in the conventional T2 WIs.

This study is a prospective study. 60 patients (28 males and 32 females, mean age 49.97 ± 11.62) referred from the neurology and neurosurgery outpatient clinics with neurological symptoms and signs of cervical compressive myelopathy with cervical spondylotic changes and normal cord signal on conventional T2 WIs were included in this study between November 2020 and December 2021. The clinical severity of compressive myelopathy was graded based on the modified Japanese Orthopedic Association (mJOA) score. The cervical discs were categorized according to their effect on the cervical cord (disc severity). MR diffusion tensor imaging was done for all patients; FA and ADC parameters opposite all cervical discs were measured. FA & ADC values of the cervical cord at level of most severe disc lesions and at non-stenotic level (C2-3, considered as internal reference) were compared. The DTI parameters at level of most severe disc lesions were also correlated with disc severity and mJOA score. The local ethical committee approved this prospective study with written informed consent was taken.

Inclusion criteria:

- Patients with clinical symptoms and signs of cervical compressive myelopathy (neck pain, upper limb tingling, numbness ± weakness and bladder dysfunction).
- Conventional MR imaging with cervical spondylotic changes.
- Normal cervical cord signal on conventional T2 WIs.
- Any age or sex.

Exclusion criteria:

- Other causes of cervical compressive myelopathy (e.g. neoplastic, spondylodiscitis).
- Previous cervical spine surgery.
- Presence of cervical cord intra-medullary hyperintensity on T2 WIs.
- Contraindications of MRI (e.g. claustrophobic, MR incompatible cardiac pacemakers or prosthetic cardiac valves).

Each patient included in the study was subjected to:

- Full history taking.
- General and neurological examination by the referral doctor with mJOA score categorization.
- MRI diffusion tensor imaging of the cervical spine.

Modified Japanese Orthopedic Association (mJOA) score:

All patient were thoroughly evaluated, with their neurological status (motor, sensory and sphincteric) was documented. The clinical severity of compressive myelopathy symptoms was graded based on the mJOA score. mJOA is a clinical function scoring system for assessing functional status in patients with cervical myelopathy. It evaluates motor function both in upper and lower extremities, sensory function in the upper extremity as well as bladder function. Each scale ranges from 0 to 7, 5, 3, and 3 respectively. The total score is of 18. The clinical severity of myelopathy was defined according to Fehlings et al., 2013 [4] as follows:

- Mild: The mJOA score is 15 or higher.
- Moderate: The mJOA score is 12 to 14.
- Severe: The mJOA score is less than 12.

MR and DTI methodology:

The MRI protocol at our institution was performed using a 1.5-T unit (Toshiba Vantage Titan closed machine) without prior preparation or anesthesia. Patients were examined in the supine position head first and earplugs were offered. A standard cervical coil was used with neck extension.

The sequences obtained were axial T2-FFE WI, sagittal T1 and T2 WIs and diffusion tensor imaging (DTI) high- SENSE consisted of: A fat-suppressed single-shot spin echo-planar sequence in 33 encoding directions. B-value=0 & 800 s/mm^2 (Table 1).

Table (1): Parameters of MR pulse sequences.

Sequence	TR	TE	Matrix	FOV	Flip angle	Slice thickness	Acquisition plane
T1	400	8	176x200	250	90	3.5/1	Sagittal
T2	3000	120	176x200	250	90	3.5/1	Sagittal
T2-FFE	495	10	132x129	150	25	4.0/0.6	Axial
DTI	2800	100	80x108	250	90	2.0/0.0	Sagittal

Images were transferred to the workstation (Toshiba Magnetic Resonance (MR) Virtual Explorer Workstation) supplied by the manufacturer.

Processing:

- Initially: The anatomical and pathological evaluation of the cervical spine and cervical cord was done in the axial and sagittal T1 and T2 WIs for detection of compressive spondylotic disc lesions and any abnormal cord signal.
- We categorized the cervical discs according to their effect on the cervical cord (disc severity) into:
  - Discs touching the cord without indentation (deformation) of the cord.
  - Discs indenting (deforming) the cord.
- DTI images were then processed using the Toshiba software for DTI to obtain color-coded images in the axial and sagittal planes.
- The color-coded images were reviewed to detect any abnormality in the form of color change in the normal blue code of the normally oriented cranio-caudal cervical cord white matter tracts fibers.
- Thereafter; multiple circular regions of interest (ROIs) were manually plotted within the cervical cord in the axial combined anatomical and color-coded images opposite all cervical discs levels after magnification of the images to include the entire cervical cord cross section. We paid special attention to exclude any surrounding CSF to avoid CSF partial volume effect.
- FA & ADC values of all ROIs opposite cervical discs were generated.
- MR Tractography using multi-ROI technique was then performed; and the workstation software algorithm tracked the white matter tracts that passed through these plotted ROIs.

Interpretation: (Figs. 1,2)

- Color-coded DTI maps and tractography of the cervical cord were analyzed.
- FA and ADC values of the cervical cord opposite the level of most severe disc lesions were compared with that at non-stenotic level C2-3 (considered as internal reference/control due to the relative stability of the upper cervical spine and the lack of related significant discal lesions) to reduce the variability of FA & ADC values related to different gender and ages. The DTI parameters at the level of most severe disc lesions were also correlated with the disc severity and mJOA score.
- The cervical compressive myelopathy was diagnosed in DTI images by the identification of any change in the normal blue color-code of the normally oriented cranio-caudal cervical cord white matter tracts fibers and/or by reduced FA value or increased ADC value of the cervical cord opposite the most effective disc lesion compared to the non-stenotic C2/3 reference level.

√	c2-3	10	0.826±0.121	0.706±0.181
√	c3-4	18	0.663±0.222	0.975±0.517
√	c4-5	15	0.665±0.151	0.859±0.263
√	c5-6	8	0.631±0.137	1.112±0.482
√	c6-7	9	0.665±0.120	0.894±0.174
√	c7-d1	8	0.651±0.175	0.800±0.178

Fig. (1): A 40-year-old female patient presented with neck pain and left brachialgia. Sagittal T2 MRI WI showed C5-6 posterior and bi-posterolateral osteo-discal lesion seen touching the ventral aspect of the cervical cord without evident cord deformation (score 1) and normal T2 cord signal. Moderate severity on mJOA score (score 14). Sagittal color-coded image and tractography showed preserved normal blue color code opposite the affected disc. FA & ADC values at C5-6 level were 0.631 & 1.112 compared to 0.826 & 0.706 at C2-3 reference level respectively.

√	C2/3	14	0.675±0.239	0.644±0.384
√	C3/4	13	0.562±0.102	0.635±0.200
√	C4/5	11	0.516±0.151	0.977±0.202
√	C5/6	17	0.591±0.172	0.934±0.256
√	C6/7	13	0.577±0.215	0.914±0.212
√	c7/d1	13	0.621±0.099	0.747±0.173

Fig. (2): A 34-year-old male patient presented with neck pain and bilateral lower limb weakness. Sagittal T2 MRI WI showed C3-4 posterior disc lesion seen indenting (deforming) the ventral aspect of the cervical cord (score 2) with normal T2 cord signal. Moderate severity on mJOA score (score 12). Sagittal color-coded image and tractography showed preserved normal blue color code opposite the affected disc. FA & ADC values at C3-4 level were 0.562 & 0.695 compared to 0.675 & 0.644 at C2-3 reference level respectively.

Statistical methods:

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between values measured at stenotic and non-stenotic levels were done using paired *t*-test [5]. Correlations between quantitative variables were done using Pearson correlation coefficient [6]. *p*-values less than 0.05 were considered as statistically significant.

Results

A total of 60 patients presented with neurological symptoms and signs of cervical compressive myelopathy were included in this study with the mean patient age was (49.97±11.62) years old; ranged between 25 and 70 years. 28 of patients were males (46.7%) and 32 were females (53.3%).

Regarding the clinical function score (mJOA score): 16 patients were graded as mild (26.7%), 31 as moderate (51.7%) and 13 as severe (21.6%) (Fig. 3).

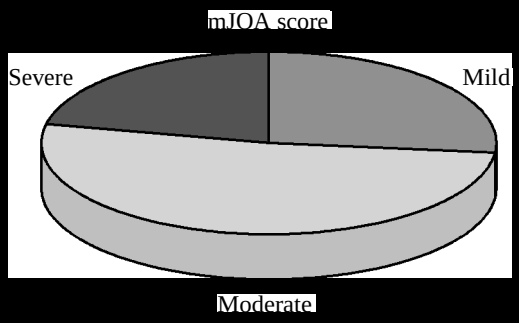

Fig. (3): mJOA score distribution in study group.

Regarding the most severe (effective) disc: C5-6 was the most effective disc in 29 patients (48.3%), C4-5 in 13 patients (21.7%), C6-7 in 11 patients (18.3%) and C3-4 in 7 patients (11.7%) (Fig. 4).

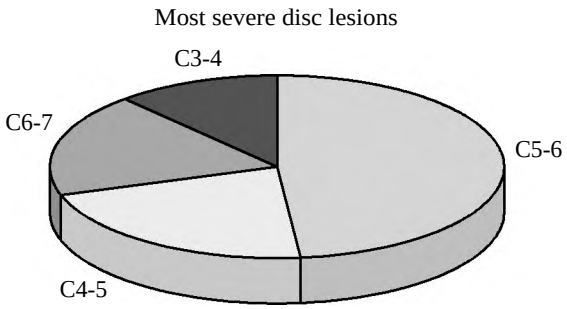

Fig. (4): Distribution of most severe disc lesions in study group.

Regarding the severity of most effective disc lesions: 24 cases (40%) had disc lesions that touched the cord without indentation and 36 cases (60%) had disc lesions that indent (deform) the cervical cord.

Regarding FA parameter. At the level of most severe disc lesions; we found statistically significant reduction of FA values compared to non-stenotic C2-3 reference level with p-value <0.001. The mean FA value at level of most severe disc lesions was (0.57±0.10) compared to (0.67 ±0.06) at non-stenotic reference level (Table 2, Fig. 5).

Regarding ADC parameter. At the level of most severe disc lesions; we found statistically significant increase of ADC values compared to non-stenotic reference level with p-value 0.015. The mean ADC value at level of most severe disc lesions was (1.02 ±0.34) compared to (0.88±0.31) at non-stenotic reference level (Table 2, Fig. 6).

Table (2): Differences in FA & ADC parameters opposite most severe disc lesions and at non-stenotic level.

	Mean	Standard deviation	Minimum	Maximim	p-value
- FA at non stenotic level	0.67	0.06	0.60	0.83	<0.001
- FA at most severe disc lesions	0.57	0.10	0.44	0.83	
- ADC at non stenotic level	0.88	0.31	0.22	1.42	0.015
- ADC at most severe disc lesions	1.02	0.34	0.09	1.44	

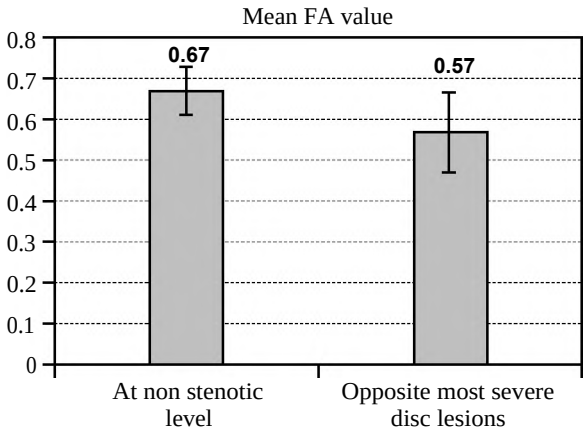

Fig. (5): Differences in mean FA opposite most severe disc lesions and at non-stenotic level.

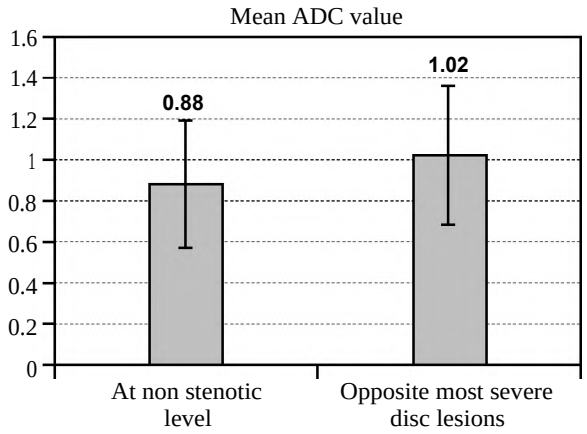

Fig. (6): Differences in mean ADC opposite most severe disc lesions and at non-stenotic level.

Regarding the sensitivity of DTI parameters for detection of myelopathy (Fig. 7): FA parameter: 52/60 cases showed myelopathy (sensitivity =86.66%). ADC parameter: 48/60 cases showed myelopathy (sensitivity=80%).

Both FA and ADC parameters show significant correlation with disc severity (p-value <0.001 & 0.008 respectively) (Table 3).

Both FA and ADC parameters show significant correlation with mJOA score (p-value 0.015 & 0.031 respectively) (Table 3).

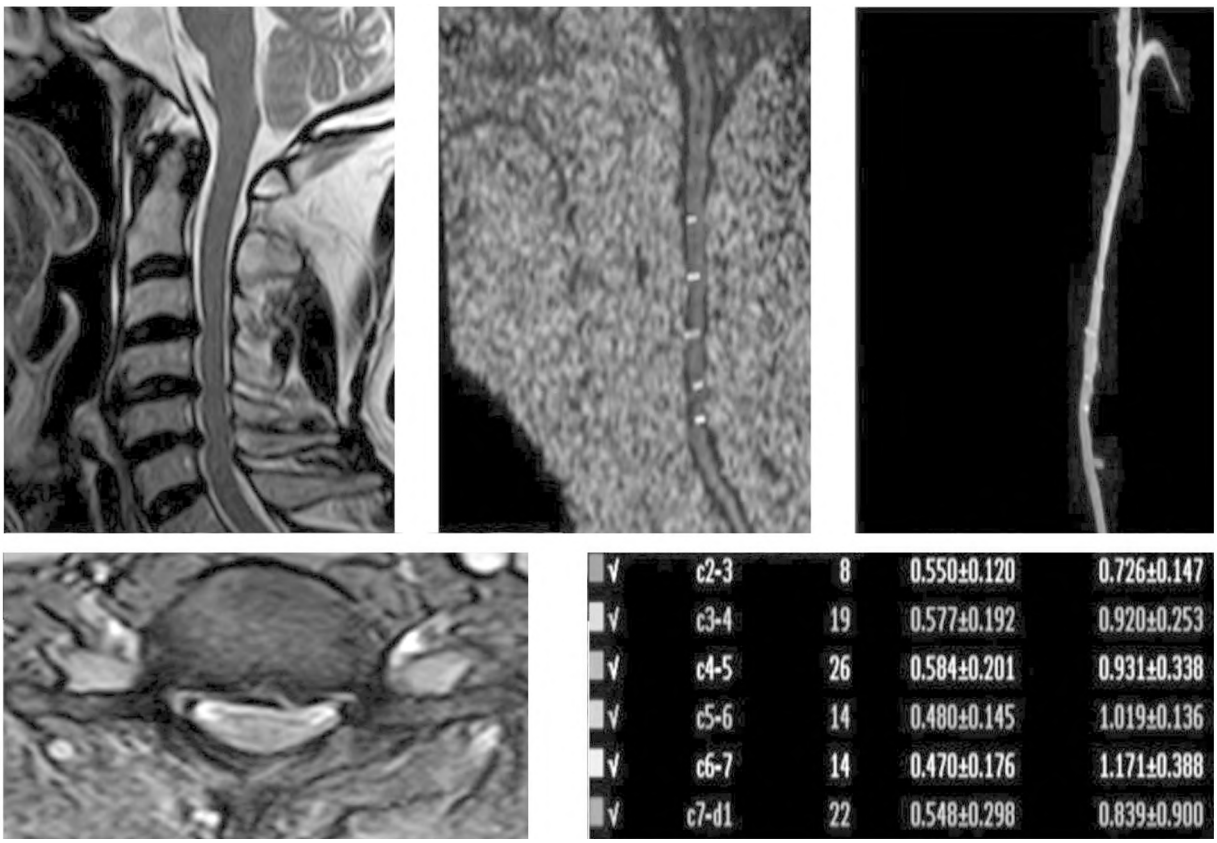

Fig. (7): A 63-year-old male patient presented with neck pain and left brachialgia. Sagittal T2 MRI WI showed multi-level posterior discs lesions with the most effective at C5-6 level seen indenting the left ventrolateral aspect of the cord (score 2) with normal T2 cord signal. Moderate severity on mJOA score (score 13). Sagittal color-coded image and tractography showed preserved normal blue color code opposite the affected disc. FA & ADC parameters at C5-6 level are 0.480 & 1.019 compared to 0.550 & 0.726 at C2-3 reference level respectively.

Table (3): Correlation between FA & ADC parameters, disc severity and mJOA score.

		FA opposite most severe disc lesions	ADC opposite most severe disc lesions
Disc severity	*p*-value	<0.001	0.008
mJOA score	*p*-value	0.015	0.031

Discussion

CSM is a major cause of motor dysfunction. MRI is important for identification of spinal cord compression. Intra-medullary high T2 WIs signal intensity could reflect pathological changes in the cervical cord (myelopathy). However; such intra-medullary T2 signal abnormalities alone are not sensitive enough to detect early myelopathic changes or to quantify the degree of spinal cord injury; as they frequently appear in the late period of the clinical course of cervical spondylotic myelopathy and often associated with poor prognosis and unfavorable post-operative outcome **[7]**.

The radiological diagnosis of CSM has to be made as early as possible, since surgical interference in earlier stages during the disease course was reported to be more successful and associated with favorable post-operative clinical outcome when compared with later stages **[1,8]**.

The purpose of this study was to investigate the utility of MR diffusion tensor imaging using its quantitative FA and ADC parameters as an early detector biomarker of microstructural cord changes in cervical spondylotic myelopathy (CSM) patients with no detectable intramedullary hyperintensity on the conventional T2 WIs.

This study is a prospective study. 60 patients (28 males and 32 females, mean age 49.97 ± 11.62) presented with neurological symptoms and signs of cervical compressive myelopathy with cervical spondylotic changes and normal cord signal on conventional T2 WIs were included in this study.

In our study; DTI parameters at C2-3 level were considered as internal reference/control (due to the relative stability of the upper cervical spine and the lack of related significant discal lesions) to reduce the variability of FA & ADC values related to different gender and ages. We found that

the mean FA & ADC values at non-stenotic C2-3 reference level=0.67±0.06 & 0.88±0.31 respectively. This is compatible with Toktas et al., 2016 **[9]** who reported the mean FA and ADC values at non-stenotic level=0.688 & 0.918. Chagawa et al., 2015 **[10]** & Wei et al., 2017 **[11]** also reported the normal cord FA values to be 0.68±0.05.

When we reviewed other studies, we found variability in the mean FA value of normal cord ranging from 0.74 by Hassan et al., 2019 **[12]** and Facon et al., 2005 **[13]** to 0.595 by Dina et al., 2017 **[14]** & 0.58 by Banaszek et al., 2014 **[15]**. This could be explained by the variability in methodology of measurement of FA of the normal cord among these studies; either measuring in healthy volunteers or using internal reference. Moreover; the level of measurement of FA of normal cord either upper cervical cord, lower cervical or dorsal cord contributed to the variability of mean FA of normal cord among these studies.

When we compared the FA & ADC parameters at the level of most severe disc lesions and at non-stenotic reference level; we found statistically significant reduction of FA values (mean 0.57 ±0.10 vs. 0.67±0.06 with p-value <0.001) and increase of ADC values (mean 1.02±0.34 vs. 0.88 ±0.31 with p-value 0.015) at level of most severe disc lesions. This FA reduction and ADC increase at stenotic level is likely due to axonal damage, local extracellular edema or reduction in nerve fibers with increased extracellular space. This agrees with the studies of Song et al., 2011 **[16]**, Kerkovsky´ et al, 2012 **[17]**, Hori et al., 2012 **[18]**, Hassan et al., 2019 **[12]**, Liu et al., 2020 **[19]** & Zhang et al., 2022 **[20]** which stated statistically significant FA reduction and ADC increase between stenotic and non-stenotic cord levels.

This study showed that FA & ADC parameters had higher sensitivity than conventional T2 WIs for detection of early compressive myelopathy. FA had 86.66% sensitivity & ADC 80% sensitivity for detection of early myelopathic changes in CSM patients with normal cord signal on T2 WIs. Our study results agree with Dong et al., 2018 **[21]**, Shen et al., 2018 **[22]**, Nukala et al., 2019 **[23]** & Zhang et al., 2022 **[20]** who reported that DTI quantitative parameters had higher sensitivity that conventional MRI in the detection of early compressive myelopathy. Demir et al., 2003 **[24]** reported that ADC had nearly 80% sensitivity for detecting myelopathy in patients with spinal cord compression and that DTI parameters are more sensitive than conventional T2 WIs signal in evaluating patients with CSM. d'Avanzo et al., 2020 **[25]** also reported that FA could be used as a marker of early cervical myelopathy and could represent a promising diagnostic tool in patients affected by CSM.

We found that both FA and ADC parameters show statistically significant correlation with disc severity (p-value <0.001 & 0.008 respectively). Furthermore; FA and ADC parameters also showed statistically significant correlation with modified Japanese Orthopedic Association (mJOA) score (p-value 0.015 & 0.031 respectively). This agrees with the studies of Dong et al., 2018 **[21]**, Shen et al., 2018 **[22]**, Severino et al., 2020 **[26]** & Neeraj et al., 2021 **[27]** which found a strong correlation between FA parameter and mJOA score and also reported that CSM patients with higher FA at the most stenotic level tended to have better functional recovery after cervical decompression surgery compared to those with lower FA; raising the concern for the utility of FA as both diagnostic and potential prognostic biomarker tool.

Conclusion:

MR diffusion tensor imaging using its quantitative FA and ADC parameters is more sensitivity than conventional T2 WIs in detection of early microstructural cord affection in CSM patients and could help as an early detector biomarker of cervical myelopathy before the appearance of any detectable signal abnormalities on T2 WIs. Our study enhanced the utility of DTI in cases with CSM to solve the clinical/radiological mismatch; enabling the decision of appropriate timing of cervical decompression surgery before the chronic irreversible myelopathy changes become settled.

Study limitations:

First; the relatively long scan acquisition time and processing as well as low signal-to-noise ratio are still limitations for the use of DTI for screening of patients with CSM. The use of 3-T MR scanners could shorten the scan time and improve the signal-to-noise ratio. Second; there was no pathological correlation, so the myelopathic changes become an assumption. Finally; the prognostic value of DTI for post-decompression surgery functional improvement wasn't evaluated. Future studies on the role of DTI to prognosticate CSM is recommended.

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هل يستطيع الرنين المغناطيسى الإنتشارى للألياف العصبية المساعدة فى حل عدم التوافق الإكلينيكى الإشعاعى فى مرضى الإعتلال النخاعى للحبل الشوكى العنقى؟

يمثل الإعتلال النخاعى للحبل الشو كى العنقى الناتج عن ضغط الغضاريف تحدياً إكلينيكياً وإشعاعياً بسبب عدم التوافق بين العرض المرضى ونتائج الرنين المغناطيسى التقليدية.

تعتبر تقنية التصوير بالرنين المغناطيسى الإنتشارى للألياف العصبية تقنية واعدة فى الكشف عن التغيرات المبكرة للحبل الشوكى قبل إكتشافها فى صور الرنين المغناطيسى التقليدية.

فى دراستنا قمنا بتقييم قدرة الرنين المغناطيسى الإنتشارى للألياف العصبية على التشخيص المبكر لحالات الإعتلال النخاعى للحبل الشوكى العنقى إشعاعياً رغم عدم وجود أى تغيرات فى صورة الحبل الشوكى فى فحوصات الرنين المغناطيسى التقليدية.

وقد وجدنا أن متوسط قيمة تباين الكسور فى الحبل الشوكى الطبيعى هى ٠.٠٦٧.

ولقد توصلنا لنتائج تؤ كد على أن قدرة الرنين المغناطيسى الإنتشارى للألياف العصبية على تشخيص حلات الإعتلال النخاعى للحبل الشوكى العنقى أعلى من قدرة فحص الرنين المغناطيسى التقليدى (بدرجة حساسية ٨٦.٦٦٪)، وتوصلنا إيضاً لنتائج ذات دلالة إحصائية عالية على وجود ربط بين الإنخفاض فى قيم تباين الكسور مع درجة التأثر الوظيفى للمريض.

وفى الختام توصى الدراسة بإضافة فحص الرنين المغناطيسى الإنتشارى للأ لياف العصبية لفحص الرنين المغناطيسى التقليدى مما قد يفيد فى التشخيص الباكر لإعتلال النخا ع الشو كى، للمساعدة على إتخاذ القرار العلاجى السليم والتدخل الجراحى فى الو قت المناسب مما يحسن من نتائج العلاج على مستوى الاداء الوظيفى للمريض.