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A diagnostic biomarker for cervical myelopathy based on dynamic MRI

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Running head: Myelopathy prediction using dynamic DTI
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Key Points

- Diffusion tensor imaging (DTI) in neck extension may improve the diagnosis of degenerative cervical myelopathy (DCM) and provide an imaging biomarker for the detection of DCM.
- When comparing clinical myelopathy patients with visible intramedullary hyperintensity (IHIS) on T2-weighted imaging with patients without IHIS sign, significant increases in ADC values between the control and the pathological segments were found for both groups in extension only.
- Our findings serve as a diagnostic tool to possibly identify early changes in the spinal cord related to myelopathy and to indicate potentially reversible spinal cord injury and support the indication for surgery in select cases.

Abstract

Study design: Multicenter prospective observational study

Objective: Diffusion tensor imaging (DTI) in flexion-extension improves the diagnosis of degenerative cervical myelopathy (DCM). We aimed to provide an imaging biomarker for the detection of DCM.

Summary of background data: DCM is the most common form of spinal cord dysfunction in adults; however, imaging surveillance for myelopathy remains poorly characterized.

Methods: Symptomatic DCM patients were examined in maximum neck flexion-extension and neutral positions in a 3T-MRI scanner and allocated to two groups: i) patients with visible intramedullary hyperintensity (IHIS) on T2-weighted imaging (IHIS+, n = 10); and ii) patients without IHIS (IHIS-, n = 11). Range of motion, space available for the spinal cord, apparent diffusion coefficient (ADC), axial diffusivity (AD), radial diffusivity (RD), and fractional anisotropy (FA) were measured and compared between the neck positions and between the groups as well as between control (C2/3) and pathological segments.

Results: Significant differences between the control level (C2/3) and pathological segments were appreciated for the IHIS+ group at neutral neck position in AD; at flexion in ADC and AD; and at neck extension in ADC, AD, and FA values. For the IHIS- group, significant differences between the control level (C2/3) and pathological segments were found only for ADC values in neck extension. When comparing diffusion parameters between groups, RD was significantly different in all three neck positions.

Conclusion: Significant increases in ADC values between the control and pathological segments were found for both groups in neck extension only. This may serve as a diagnostic tool to identify early changes in the spinal cord related to myelopathy and to indicate potentially reversible spinal cord injury and support the indication for surgery in select circumstances.

Introduction

Degenerative cervical myelopathy (DCM) is the most common form of spinal cord dysfunction in adults; however, imaging surveillance for myelopathy remains poorly characterized [1, 2]. Intramedullary hyperintensity (IHIS) on T2-weighted imaging reflects cord edema or myelomalacia, however, it only has a sensitivity of 60% for the detection of clinical myelopathy. The sensitivity can be increased to 80% when combining with the analysis of apparent diffusion coefficient (ADC) values [3]. The sensitivity of T2-weighted imaging can be further improved by performing dynamic flexion-extension T2-weighted imaging [4].

The use of diffusion tensor imaging (DTI) allows for the evaluation of microstructural changes in the spinal cord not otherwise detected on routine conventional MRI [5]. Schatlo et al. combined T2-weighted imaging with dynamic DTI and showed that increased ADC values in extension were the most sensible marker for suspected cervical spine stenosis based on clinical examination [6]. This additional information can be of substantial value in cases where surgical intervention is being considered.

DTI enables estimates of diffusivity within each voxel. Fractional anisotropy (FA), apparent diffusion coefficient (ADC), radial diffusivity (RD), and axial diffusivity (AD) are calculated from the diffusion tensor. ADC represents the average diffusivity, regardless of direction, whereas FA refers to the fraction of diffusion that is directionally dependent. AD, also called longitudinal diffusion, apply to the diffusivity that correspond with the direction of fastest diffusion in each voxel. In the spinal cord it aligns with the rostrocaudal orientation along the white matter tracts. RD, or transverse diffusivity, applies to the average diffusivity perpendicular to AD [7, 8].

The use of DTI in neck flexion-extension allows the degree of stenosis and the space available for the cord to be assessed between flexion-extension. This provides information regarding possible cord compression, which reflects the diffusion parameters. Although DTI in neck flexion-extension has been performed in healthy volunteers and DCM patients [6], we hypothesized that DTI is more sensitive for the detection of DCM. Here, we examined patients with clinical myelopathy symptoms and visible IHIS sign (IHIS+) vs patients with clinical myelopathy symptoms without IHIS sign (IHIS-

), to see whether the MR in neck extension-flexion combined with T2-weighted imaging and extended DTI parameters (ADC, AD, RD, and FA) can be used as an imaging biomarker for clinical myelopathy.

Methods

Subjects

In this prospective, multicenter study we examined patients with suspected cervical spine stenosis based on clinical examination. The study was approved by the local ethics committee and all subjects provided written informed consent for participation.

Inclusion criteria consisted of pain in the neck and back and additionally, one or more of the listed symptoms: tingling, numbness or weakness with decreased fine motor skills, pathological reflexes in extremities (e.g. clonus, Babinski, Hoffman's sign), walking difficulties including ataxia and gait disturbances, spastic quadriplegia, sensory loss and bladder-bowel disturbances. All the patients had these symptoms for at least 6 weeks prior the MRI examination. The modified Japanese Orthopedic Association (mJOA) score [9, 10] and DCM classification [4] were completed. Excluded patients were those with prior inflammatory nervous system disease, absence of the above mentioned clinical signs, significant neck trauma, prior spinal surgery, or were below 18 years of age at the time of study inclusion.

MRI

Patients underwent neurological examination in neck flexion-extension and were eligible for MRI if no neurological deficit occurred during this workup. Spinal MRI was performed on a 3T Magnet Resonance Imaging Scanner (Skyra, Siemens Healthcare, Erlangen, Germany) using 20-channel head and spine coil in flexion, extension, and neutral neck positions. The dynamic examination was performed with as much active neck flexion-extension as possible without discomfort, as described earlier [6]. Head and shoulders were stabilized using padding and cushions. We did not attempt to

achieve standard predetermined positions but instead allowed each patient to find a comfortable position within the head coil.

All sequences were performed in flexion, extension and neutral neck positions. The imaging protocol included sagittal T2-weighted turbo spin echo (TSE) sequence (acquisition time [TA] of 3:20 min, repetition time [TR] of 3,500 ms, echo time [TE] of 126 ms, echo train length of 19, slice thickness of 3 mm, spacing between the slices of 0.3 mm, 1.1 mm in-plane resolution, and 1 average) as well as sagittal RESOLVE DTI sequence (TA = 4 min, TR = 1,700 ms, TE = 62 ms, 3 mm slice thickness, 2 averages, b values of 0 and 750 s/mm^2, 30 diffusion directions, 1.5 x 1.5 mm2 voxel size resolution in x and y direction). Based on the MRI examination, the patients were divided into two groups (Fig. 1): i) IHIS+, n = 10; and ii) IHIS-, n = 11. The baseline characteristics are summarized in Table 1.

Data analysis

The sagittal T2-weighted images were examined by an experienced neuroradiologist for possible cervical stenosis, spinal cord atrophy, and focal or diffuse signal abnormalities. Midsagittal disk-level spinal canal diameters from the lower endplate of C2 to the lower endplate of C7 were measured at the level of each disc (space available for the cord, shown in mm) from the T2-weighted sagittal images. Central canal compression was graded according to the Muhle classification [4]. The angle between a line parallel to the lower endplate of C2 to the lower endplate of C7 served as a measure of angulation (Cobb angle). Range of motion was determined as the difference in the angulation between flexion and extension. Further, T2-weighted images were used to divide the patients in two groups: with/without visible intramedullary hyperintensity (IHIS+/IHIS-).

ADC, AD, RD, and FA values were determined using Siemens syngo.via Neuro-3D software (Siemens Healthcare, Erlangen, Germany). Fiber tracking uses mathematical models to reveal the main direction of the fibers according to a voxel-by-voxel based analysis using the directional information of the largest eigenvector of the diffusion tensor [11]. Deterministic fixed step tracking algorithm, which uses the directional information described by the diffusion tensor, was used. It uses a Gaussian model for DTI, but one which does not imply that there is only one fiber population per voxel. The model spreads several seeds per voxel and takes the neighboring DTI voxel information

into account by interpolation [11]. For stopping criterion the following parameters were used: seeding threshold FA, 0.10; step size, 0.5 mm; stopping criteria for tracking FA, 0.10; and deflection angle, 60^{o}.

The freehand region of interest for the diffusion parameter measurements was the spinal cord at a length of 10 mm on a midline section centered on the disc space, covering the whole A-P dimension of the cord in the sagittal plane, as described in detail by Schatlo et al. [6]. Measurements were obtained at a control level (defined as C2/3 which was never affected by stenosis or myelopathy) and at levels affected by stenosis (C3/4 to C6/7, varying case by case).

Statistical analysis

Statistical analysis was performed using the SPSS 21.0 statistical package (IBM, Armonk, NY, US). Paired t-test was used to determine the statistically significant differences ($p < 0.05$) between the control level (C2/3) vs pathological segments (case dependent). In case of several pathological segments, each were separately compared to the control values at C2/3. Mixed effect ANOVA was performed to see whether there are main effects based on with-in-subject variable (neck position in flexion/neutral/extension); between-subject variable (groups IHIS+/IHIS-) and the DTI parameters (dependent variable). A Hochberger correction was used to account for multiple comparisons. Pearson's linear correlation was performed between the age, mJOA score, and ADC values in extension.

Results

Basic parameters

Twenty-one patients (IHIS+, n = 10; IHIS-, n = 11) met inclusion criteria. No statistically significant differences were found between the groups (Table 1). The IHIS+ group included 10 patients with mean age of 55 ± 11 (range 38–66) years and BMI of 28 ± 5. The IHIS- group consisted of 11 patients with mean age of 59 ± 14 (range 37–81) years and BMI of 27 ± 6. Neck flexion-extension MRI of the cervical spine was well tolerated well by all participants and all the scans could be conducted without any interruptions.

Clinical parameters

Clinical signs of myelopathy were noted in 13 (62%) patients, sensibility disorder in 15 (71%) patients, motoric deficits in 12 (57%) patients, and chronic neck pain in six (32%) patients. The mean mJOA score was 15 ± 4 for IHIS+ 16 ± 2 and for IHIS- 15 ± 3, respectively. The segments affected by stenosis were C3/4 (50%/18%), C4/5 (30%/27%), C5/6 (30%/73%), and C6/7 (20%/26%) based on the group definitions of IHIS+/IHIS-, respectively. In total, 80% and 50% of the IHIS+ and IHIS- patients underwent decompressive surgery after the MRI examination, respectively.

Imaging findings

The overall range of motion was not significantly different between the two groups, with 36 ± 6^{o} (IHIS+) and 38 ± 12^{o} (IHIS-), respectively (Table 1.) Regarding Muhle classification [4], cord touch was revealed (score = 1) by 30% (3/10 patients) and 56% (5/9 patients) of the IHIS+ and IHIS- groups, respectively; cord compression (score = 2) was detected by 70% (7/10 patients) and 22% (2/9 patients) of the IHIS+ and IHIS- groups, respectively; and free cord (score = 0) was classified by 22% (2/9 patients) of the IHIS- group patients. Sagittal spinal canal diameters (space available for the cord) were compared across the three positions and the groups (Fig. 2). No statistically significant differences were detected between the IHIS+ and IHIS- groups or within the groups between the three positions.

Diffusion parameter analysis

Significant increase based on paired t-test between the control level (C2/3) and the pathological segments were found for the IHIS+ group at normal neck position in AD ($p < 0.05$); at flexion in ADC ($p < 0.05$) and AD ($p < 0.01$); as well as at extension in ADC ($p < 0.01$), AD ($p < 0.05$), and FA ($p < 0.05$) values. For the IHIS- group, significant increase between the control (C2/3) and the pathological segments were found only at extension in ADC ($p < 0.05$) values (Fig. 3, Table 2).

Mixed effect ANOVA revealed a main effect to be the neck position ($F = 7.650$, $p < 0.05$, $\eta^2_p = 0.29$). Between-subject IHIS+/IHIS- effect was not statistically significant ($F = 1.837$, $p = 0.191$, $\eta^2_p = 0.09$).

When comparing ADC, AD, RD, and FA values between the IHIS- and IHIS+ groups, statistically significant decrease ($p < 0.01$) in RD values was found in neutral neck position at the control level C2/3 as well as at affected level in all three neck positions (Table 2). No correlation was found between the mJOA and the ADC values in extension (r [IHIS+] = 0.37, r [IHIS-] = 0.11), however, a moderate correlation was found between the age and the ADC values in extension for the IHIS+ group (r [IHIS+] = -0.66), r [IHIS-] = 0.11). The sensitivity of ADC in neck extension for all DCM patients was 100%.

Discussion

Statistically significant increases in ADC values were found for both groups at neck extension, independent of the presence of an IHIS sign. Our finding suggests that ADC at extension may serve as a biomarker for early onset of myelopathy, since ADC values are high in early myelopathy and lower in later stages [12].

In a healthy population, no significant spinal cord narrowing is produced in neck extension an no alterations in ADC values have been reported [6]. However, when the white matter tracts are disrupted, or the permeability of axonal membranes is increased, the ADC will increase. In extension with disrupted white matter tracts, cord compression leads to reduced extracellular-space and, therefore, increased ADC values. This was also seen in our results and is in line with the current literature [3, 4, 6, 9]. It also highlights the fact that neck position is a key contributing factor when studying diffusion parameters, regardless of the IHIS sign.

Increases in ADC may indicate potentially reversible spinal cord injury [12], which is of clinical importance to prevent deterioration and permanent damage at an early time-point. Our findings are consistent with previous work indicating that ADC is of diagnostic value in the early assessment of traumatic spinal cord injury and may serve as a potential indicator of such events[13, 14].

FA is a measure of the directional dependence of the ADC, which decreases with white matter disruption. Lower FA might reflect damage to the myelin sheath surrounding axons, enlarged axonal diameter, reduced axonal packing density, or increased membrane permeability. The FA values were lower in extension in the IHIS+ group, indicating that anisotropy may be affected as well.

Further, AD values were increased in the IHIS+ group in all neck positions. This could reflect axonal injury, reduced axonal caliber, or less coherent orientation of axons. We also found decreased RD values in the IHIS+ group when compared to IHIS- in the normal position at the control level as well as at affected levels in all three neck positions. Increased RD might reflect myelin loss, loss of axons, and/or reduced axonal packing density, suggesting that the IHIS- group reflects the early onset of myelopathy more.

We acknowledge several limitations to our study: First, the sample size was relatively small and patients were not randomized. Second, due to possible discomfort to patients during the MRI examination there is a possibility for motion artefacts. However, this was minimized using padding and allowing the patient to find the maximum extension-flexion position he/she could comfortably hold during the imaging session. Therefore, we did not have to exclude any patient from the study due to motion artefacts. The groups were age-matched, but there is a possibility that age might have an impact on the ADC values. Finally, even though it has been reported that ADC does not differ from the segment level when no lesion is present [6], there remains a possibility that the segmental level might affect the ADC values. The work should be viewed as hypothesis generating as a result and further studies are needed to validate the present findings.

Even though our sample size was relatively small, our results are aligned with prior work [3, 4, 6, 12]. Increased ADC values are associated with clinical findings of neurological impairment [15-17] and potentially worse postoperative outcomes [18]. Our findings may have clinical value in diagnosing early changes of cervical myelopathy: ADC in extension could also serve as a marker in patients who might benefit from early surgical decompression. However, a study with a larger study population is needed to confirm if early surgery based on DTI data will improve clinical outcomes in patients.. In conclusion, an increase in ADC in extension may serve as a marker identifying early spinal cord changes related to cervical myelopathy. In addition, increases in ADC may indicate spinal cord injury and support the indication for surgery in select cirsumstances.

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Figure 1. Clinical myelopathy patients were divided in two groups: with (IHIS+) and without visible intramedullary hyperintensity (IHIS-) based on the normal neck position T2-weighted images. Increased ADC values were found for both groups at extension.

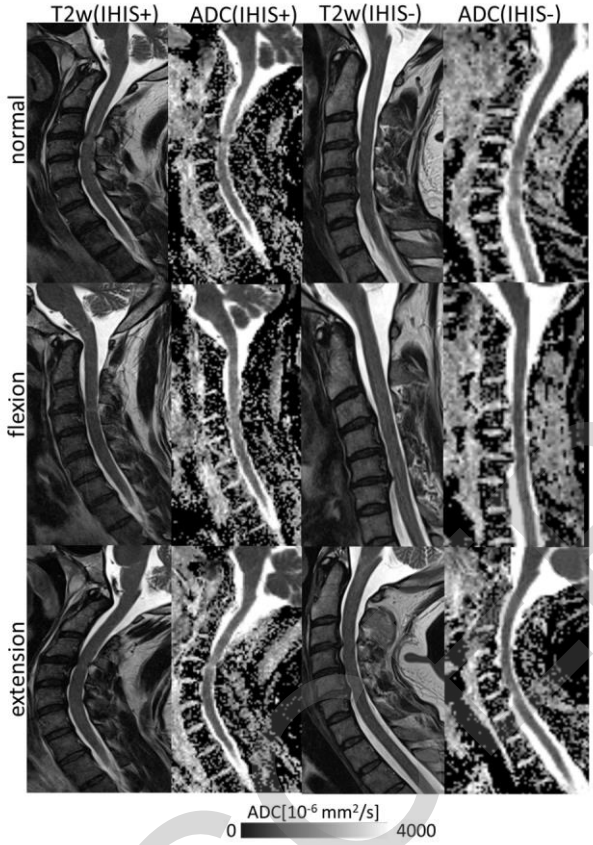
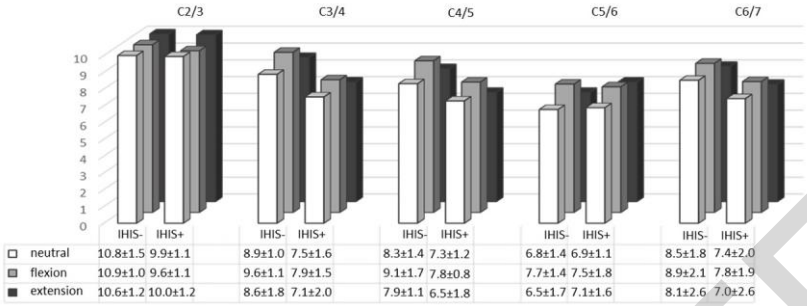


Figure 2. Sagittal spinal canal diameters (space available for the cord) for IHIS- and IHIS+ groups in neutral, flexion, and extension. No statistically significant differences were detected between the IHIS+ and IHIS- groups, or within the groups between the three neck positions.



	IHIS-	IHIS+	IHIS-	IHIS+	IHIS-	IHIS+	IHIS-	IHIS+	IHIS-	IHIS+
neutral	10.8±1.5	9.9±1.1	8.9±1.0	7.5±1.6	8.3±1.4	7.3±1.2	6.8±1.4	6.9±1.1	8.5±1.8	7.4±2.0
flexion	10.9±1.0	9.6±1.1	9.6±1.1	7.9±1.5	9.1±1.7	7.8±0.8	7.7±1.4	7.5±1.8	8.9±2.1	7.8±1.9
extension	10.6±1.2	10.0±1.2	8.6±1.8	7.1±2.0	7.9±1.1	6.5±1.8	6.5±1.7	7.1±1.6	8.1±2.6	7.0±2.6

Figure 3. Diffusion parameters of IHIS+ and IHIS- patients: controls (C2/3)marked as white and the pathological segments with black. Statistically significant differences based on paired t-test are marked (*p < 0.05, ***p < 0.01).

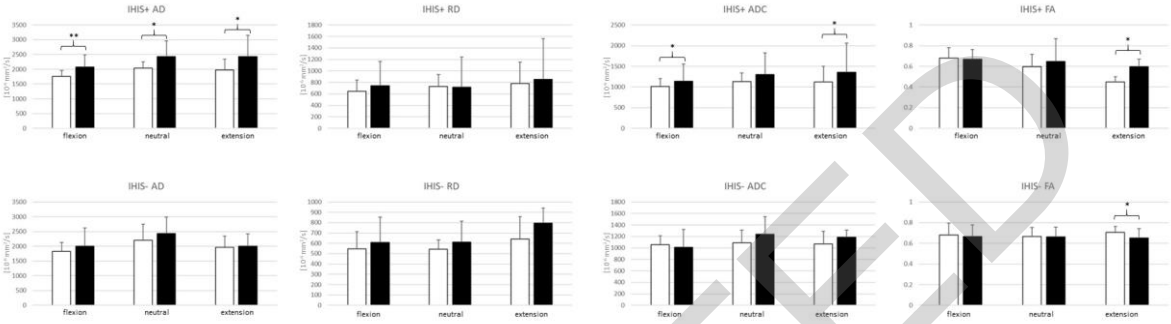


Table 1. Baseline characteristics and range of motion.

	IHIS+ (n = 10)	**IHIS- (n = 11)**
Age (years, range)	55.1 ± 11.2 (38–66)	58.7 ± 14.3 (37–81)
Female sex (n, %)	4 (40%)	6 (55%)
Weight (kg)	83.9 ± 14.9	79.2 ± 18.1
Height (cm)	169.6 ± 11.1	170.5 ± 10.8
Body mass index (kg/m^2)	27.5 ± 5.3	27.4 ± 5.1
Range of motion (^{o})	35.9 ± 5.9	37.8 ± 12.2
Angle normal position (^{o})	16.2 ± 4.2	14.8 ± 9.2
Angle flexion (^{o})	9.5 ± 3.5	10.1 ± 6.3
Angle extension (^{o})	25.3 ± 5.5	29.1 ± 7.3
mJOA* score	15.5 ± 1.5	14.7 ± 3.0
Muhle classification (0, 1, 2; %)**	0(0%), 1(43%), 2(57%)	0(27%), 1(55%), 2(18%)

Values are presented as mean ± SD.

No statistically significant differences on the baseline characteristics were detected between the groups.

*Modified Japanese Orthopaedic Association score

**Classification score: 0 = cord free; 1 = cord touched; 2 = cord compressed

Table 2. Diffusion parameters of IHIS+ and IHIS- patients.

	IHIS+ (n=10)			**IHIS- (n=11)**		
Neck position	Flexion	Neutral	Extension	Flexion	Neutral	Extension
AD [10^{-6} mm^2/s] (C/23, control)	1762±195	2036±211	1969±372	1822±310	2206±547	1966±376
AD [10^{-6} mm^2/s] (pathological level)	2076±418**	2433±527*	2433±712*	2004±615	2427±562	1996±421
RD[10^{-6} mm^2/s] (C/23, control)	644±136	727±155$^{\$\$}$	782±366	546±167	542±93$^{\$\$}$	642±217
RD [10^{-6} mm^2/s] (pathological level)	744±143$^{\$}$	714±129$^{\$}$	850±176$^{\$}$	607±146$^{\$}$	608±100$^{\$}$	710±147$^{\$}$
ADC [10^{-6} mm^2/s] (C/23, control)	1011±139	1127±80	1124±210	1054±156	1090±221	1066±221
ADC [10^{-6} mm^2/s] (pathological level)	1137±195*	1303±367	1353±351*	1008±316	1239±306	1183±129*
FA [10^{-6} mm^2/s] (C/23, control)	0.679±0.101	0.596±0.120	0.447±0.052	0.682±0.115	0.666±0.085	0.707±0.057
FA [10^{-6} mm^2/s] (pathological level)	0.668±0.095	0.648±0.219	0.595±0.073*	0.666±0.113	0.661±0.095	0.652±0.089

*****Statistically significant difference ($p<0.05$) between affected and unaffected level
******Statistically significant difference ($p<0.01$) between affected and unaffected level
$^{\$}$Statistically significant difference ($p<0.05$) between IHIS+ and IHIS- group
$^{\$\$}$Statistically significant difference ($p<0.01$) between IHIS+ and IHIS- group