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Diagnostic value of diffusion tensor imaging in patients with clinical signs of cervical spondylotic myelopathy

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ABSTRACT

Aim of the study. The aim of this study was to assess the diagnostic value of diffusion tensor imaging (DTI) in patients with symptoms of cervical myelopathy. Detailed goals included determining the diagnostic effectiveness of quantitative parameters, i.e. fractional anisotropy (FA) and apparent diffusion coefficient (ADC), in the diagnosis of cervical myelopathy, and the correlation between these parameters and clinical symptoms.

Clinical rationale for the study. The demonstration of an ischaemic focus in the spinal cord by standard magnetic resonance imaging (MRI) methods is associated with already accomplished spinal cord damage, and of course limited treatment options. Therefore, finding a new examination protocol that allows early diagnosis of myelopathic focus, before the onset of full neurological symptoms, has become a priority in the diagnosis and treatment of spine diseases. Such an examination increases the chances of correctly qualifying the patient for conservative *vs.* surgical treatment.

Material and methods. Between 2013 and 2017, 128 adults with clinical signs of cervical myelopathy were examined, and were divided into four symptomatic subgroups. A control group consisted of 37 healthy volunteers. DTI values were measured at the level of C2/C3, and at the most severe stenosis of the spine.

Results. In patients with cervical spondylotic myelopathy (CSM), the ADC values were significantly higher ($p < 0.001$), and FA values were significantly lower ($p < 0.001$), than in healthy volunteers at the stenotic level. There were significant differences in DTI parameters between the clinical subgroups ($p < 0.001$).

Conclusions and clinical implications. Changes in DTI parameters indicate a microstructural disorder of the core which is not visible in a structural MRI. FA and ADC values measured at the level of the most severe stenosis of the spinal canal allow the differentiation of patients with myelopathy of varying degrees of clinical severity. Extending standard MRI to include assessment of FA and ADC may be helpful in deciding treatment modalities (conservative *vs.* surgical) for patients with visible canal stenosis without full neurological symptoms. This may be useful in selecting patients for urgent rehabilitative treatment. This study is a starting point for further research, i.e. an evaluation of the extent of FA and ADC lesion withdrawal after surgical treatment.

Key words: cervical spondylotic myelopathy, magnetic resonance imaging, diffusion tensor imaging, spinal canal stenosis

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Introduction

Cervical spondylotic myelopathy (CSM) is the most common form of spinal cord injury. The disease usually follows a chronic course with slow progression of clinical symptoms. The cause of myelopathy is direct compression of the spinal cord through degenerated bone structures, calcified posterior longitudinal ligaments and ligamentum flavum, or hernias of the nucleus pulposus. The main clinical symptoms of cervical myelopathy include neck pain, muscle weakness in the upper and lower extremities, and parasthesia.

The main imaging method used in the diagnosis of spine diseases is magnetic resonance imaging (MRI), which depicts morphological imaging in T1, PD and T2-weighted images. It is used to present anatomical structures and pathological changes distinguished by a different signal. Morphological MRI, however, has poor sensitivity in detecting cervical myelopathy [1], as even a compressed spinal cord may have a normal signal in patients with clinical signs of damage. Abnormal signal lesions usually appear in the later stages of the disease when changes are irreversible. In many studies, it has been postulated that surgical treatment at an early stage of myelopathy is more effective than in chronic disease years after onset [2–5]. Therefore, new methods are being sought to improve the early diagnosis of myelopathy.

An opportunity to deepen the diagnosis of spinal cord diseases is represented by diffusion tensor imaging (DTI), a non-invasive magnetic resonance technique recognised as functional imaging [6]. This method is based on measurement of the movement of water molecules in the extracellular and intravascular space. In the cerebrospinal fluid, this movement is free and water molecules move at the same speed in all directions, while in the nervous tissue the movement of water molecules occurs mainly along nerve fibres, which results in a preference for one direction [7, 8]. Diffusion in tissues, in which an anatomical structure impedes the direction of movement of water molecules, is called anisotropic diffusion, and tracking of the targeted movement of water microparticles allows for the indirect imaging of fibres [7, 8]. If the fibre is broken, movement at the site of damage is disturbed, which can be seen in a DTI image [9].

Quantitative analysis of nerve fibres can be performed using the fractional anisotropy (FA) parameter and the apparent diffusion coefficient (ADC). The FA parameter ranges from 0 to 1 [10]. The white matter of the spinal cord is characterised by a high degree of organisation, so the preferred movement of water molecules takes place parallel to the course of axons, i.e. in one direction. If diffusion takes place unidirectionally, the FA value approaches 1, whereas the FA coefficient equals 0 for isotropic diffusion (i.e. free in all directions) [11]. Damage and degradation of white matter tracts will result in a decrease in the FA value.

The second helpful parameter is the ADC, which quantitatively expresses the free diffusion of water molecules in the extracellular space of the tissue and is expressed in mm^2/s. Changes in the value of this coefficient are proportional to the intensity of diffusion in a given area. In fact, in the white spinal cord, due to diffusion barriers such as cell membranes and axon myelin sheaths, the movement of water molecules is limited.

When the cell membrane loses its integrity, the movement of water molecules is freer, which should result in an increase in the ADC value. An additional application is a diffusion tensor tractography, which provides a three-dimensional graphical representation of waterways in the white matter [12] (Fig. 1).

Several studies [13–27] have shown changes in DTI parameters in the location of the greatest stenosis compared to control groups; in all of these studies, the spinal cord demonstrated an abnormal signal, indicating that changes were irreversible.

However, we have found only two studies comparing DTI values at the level of maximum cord compression in the study group and at the corresponding level in the control group, in which the spinal cord did not show signal changes.

The aim of the present study was to assess the diagnostic value of diffusion tensor imaging in patients with cervical myelopathy symptoms, but without any changes on T2-weighted images of the spinal cord. Detailed goals include determining the diagnostic effectiveness of quantitative parameters, i.e. FA and ADC, in the diagnosis of cervical myelopathy, and the correlation of these parameters with clinical symptoms. The research hypothesis assumes that imaging with a diffusion tensor is a more sensitive method than morphological MRI in patients with cervical myelopathy symptoms.

Material and methods

Material

Our study involved a group of 128 adults (86 women and 42 men, average age 53 years, range 28 to 79) with clinical signs of cervical myelopathy, who reported to the Department of Radiology at the Medical University of Gdansk for diagnosis between 1 September 2013 and 31 December 2017. The control group consisted of 37 volunteers (24 women and 13 men with an average age of 49, range 27 to 74). The Ethics Committee of the Medical University of Gdansk approved the study. Informed consent was obtained from all participants.

Inclusion criteria were clinical signs of cervical myelopathy. Exclusion criteria were as follows: contraindications for magnetic resonance imaging (i.e. claustrophobia, the presence of a pacemaker or other device containing electronic components), cervical spine injury, spinal radiation therapy, the presence of cervical spinal tumours, previous surgical treatment, and any increased signal on T2-weighted images of the cervical spine.

To assess the severity of clinical symptoms, the Japanese Orthopaedic Association score (JOA) was used. This score

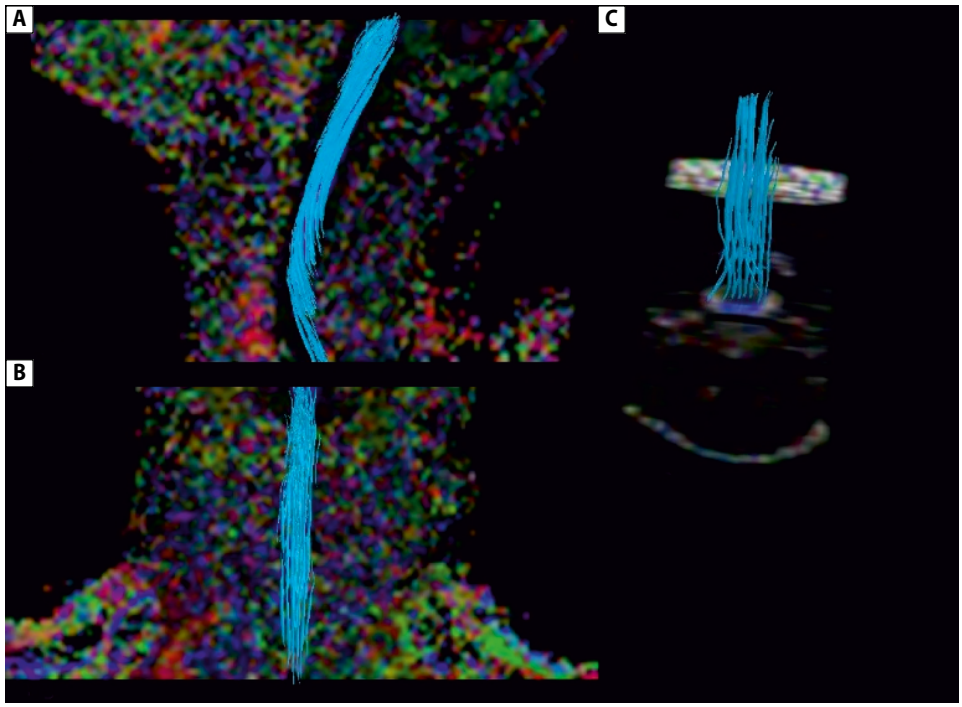

Figure 1. Diffusion tensor tractography; (**A**) sagittal plane; (**B**) coronal plane; (**C**) 3D reconstruction of spinal cord fibre tracts

comprises four sections: assessment of upper limb function (0–4 points), assessment of lower limb function (0–4 points), sensation assessment (upper limb: 0–2 point, lower limb: 0–2 points, neck: 0–2 points), and assessment of bladder function (0–3 points). The final results are presented on a scale on which values can be from 0 to 17 points.

Based on the number of JOA points, the severity of clinical symptoms was estimated, and the subjects were divided into four subgroups: those without clinical symptoms at the time of the study (17 points, 37 people), and those with mild (13–16 points, 45 people), moderate (9–12 points, 42 people), and severe (0–8 points, 41 people) cervical myelopathy.

Methods

Imaging protocols

The MR examinations were performed on a 3 T MRI scanner (Achieva TX, Philips Medical Systems, Eindhoven, The Netherlands) using a 16-channel neurovascular coil in the axial and sagittal planes and a 15-direction single-shot echo-planar imaging (EPI)-based DTI sequence in the axial plane.

The spin-echo acquisition images were acquired using the following parameters: sagittal T2-weighted sequences (slice thickness: 3 mm, FOV: 250 mm, inter-slice gap: 0.3 mm, TR/TE 3,300/100 ms, matrix 70 x 100 mm) and axial T2-weighted sequences (slice thickness: 3 mm, inter-slice gap: 0 mm, FOV: 220 mm, TR/TE 3,000/100 ms, matrix, 90 x 110 mm), sagittal T1-weighted sequences (slice thickness: 3 mm, FOV: 250 mm, inter-slice gap: 0.3 mm, TR/TE 500/8 ms, voxel: 70 x 100) and STIR sagittal planes (slice thickness: 3 mm, inter-slice gap: 0.3 mm, FOV: 250 mm, TE 65 ms, TR/TI: 2,500/220 ms, matrix: 70 x 100 mm).

The spin-echo proton density weighted acquisition images with the following parameters: axial (TR/TE 1500/8 ms, slice thickness: 3 mm, FOV: 250 mm, inter-slice gap: 0.3 mm, matrix: 70 x 100 mm). The parameters of the DTI sequence were: TR/TE 6500/68, slice thickness: 2 mm, FOV: 220 mm, inter-slice gap: 0 mm, matrix: 200 x 200 mm, b value 0 s/mm^2 and 800 s/mm^2)

Region of interest

The values of ADC and FA were determined on the basis of measurements from the region of interest (ROI), which was drawn manually in the whole area of the spinal cord including the grey and white matter, on axial images with isotropic diffusion (Fig. 2). Special care was taken to avoid the surrounding cerebrospinal fluid. ROIs were measured at the intervertebral level C2/C3 and in the location with the most severe stenosis of the cervical spine. In controls without any stenosis, the DTI parameters were measured at the C5/C6 level because this was the most common level of stenosis in patients.

Statistical analysis

All raw data for each group was presented with their number and basic descriptive statistics as mean ± standard deviation. The normality of data sets was verified using the Shapiro-Wilk test or Q-Q plots. Differences between variables were examined by proper t-tests or ANOVA with a post-hoc HSD Tukey test. To assess the interdependence between the

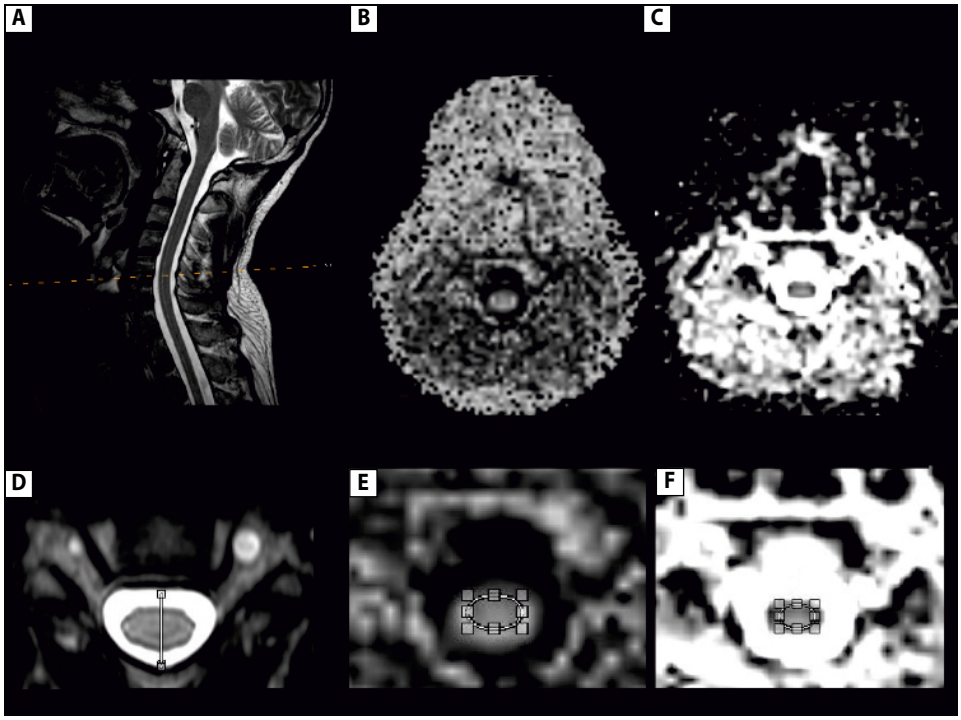

Figure 2. (**A**) Sagittal T2-weighted image showing cervical spinal cord. Referring to T2-weighted sagittal anatomical images, one slice of diffusion tensor imaging was obtained at severe stenosis of cervical spine (in patients) or at C5/C6 level (in control group); (**B**) Examples of Apparent Diffusion Coefficient (ADC) map; **C.** Fractional Anisotropy (FA) map-axial plane; (**D–F**) Measurements of spinal cord in axial plane: (**D**) placement of AP diameter, T2-weighted image; (**E**) placement of ROI, ADC map; (**F**) placement of ROI, FA map

analysed variables, Pearson's correlation coefficients were calculated. The level of significance was set at $\alpha = 0.05$. All raw data was analysed using the statistical software Statistica *vs.* 13.1 (Dell Inc. 2016).

Results

There were no statistically significant differences between groups in terms of age ($p = 0.151$) or in terms of sex ($p = 0.947$).

Comparison of DTI parameters between patients and healthy subjects

The ADC values in patients with CSM were significantly higher ($p < 0.001$) than in healthy volunteers at the stenotic level (1.04 ± 0.13 *vs.* $0.88 \pm 0.12 \times 10^{-3}$ mm^2/s), while the FA values in patients with CSM were significantly lower ($p < 0.001$) than in healthy volunteers at the stenotic level (0.56 ± 0.07 *vs.* 0.62 ± 0.08). No significant differences in either FA or ADC were found at C2/C3 between patients and volunteers.

Comparison of DTI parameters between stenotic and non-stenotic levels

In patients, the ADC value at the narrowed level was significantly higher ($p < 0.001$) than at the C2/C3 level ($1.00 \pm 0.14 \times 10^{-3}$ mm^2/s *vs.* $0.91 \pm 0.10 \times 10^{-3}$ mm^2/s). Conversely, at the stenotic level, there was a significant reduction ($p < 0.001$) in FA values compared to the C2/C3 level (0.58 ± 0.08 *vs.* 0.67 ± 0.08).

Comparison of DTI parameters between clinical subgroups

There were significant differences in the DTI parameters between clinical subgroups. The ADC was significantly decreased in the control subgroup compared to other subgroups ($p < 0.001$), as well as in the mild subgroup compared to the moderate subgroup ($p = 0.001$). Conversely, there was a significant increase in FA values between the control subgroup and the moderate subgroup ($p = 0.006$), as well as between the control and severe subgroups ($p < 0.001$). Results are presented in Table 1 and Figures 3 and 4.

The analysis showed a negative correlation between the ADC value and the JOA scale with the most severe stenosis level (Pearson correlation coefficient $r = -0.545$); i.e. with a decrease in the JOA score, the ADC values increased ($p < 0.001$). In addition, the analysis showed a positive correlation between the FA value and the JOA scale at the narrowed level of stenosis (Pearson correlation coefficient $r = 0.412$), i.e. with an increase in the JOA score, the FA values increased ($p < 0.001$)

Table 1. Correlation between ADC and FA values at narrowed level and JOA measurements. Data presented as mean ± SD. P < 0.05 *vs.* [a]control, [b]mild, [c]moderate and [d]severe

	Control (n = 37)	Mild (n = 45)	Moderate (n = 42)	Severe (n = 41)	P-value
FA	0.62 ± 0.08[c,d]	0.58 ± 0.08	0.56 ± 0.08[a]	0.55 ± 0.06[a]	< 0.001
ADC	0.88 ± 0.12[b,c,d]	0.99 ± 0.14[a,d]	1.03 ± 0.11[a]	1.09 ± 0.12[a,b]	< 0.001

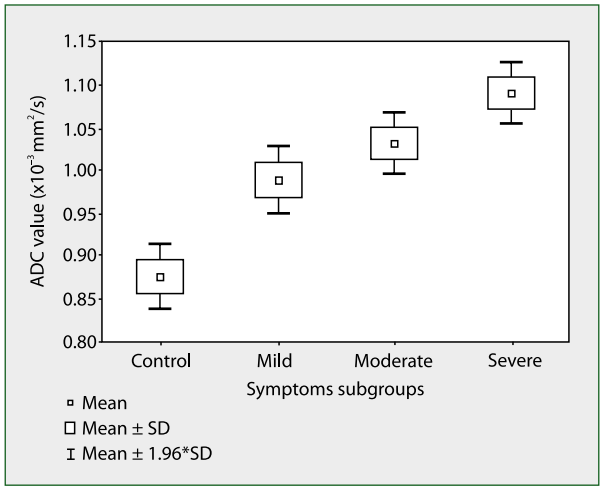

Figure 3. Mean ADC values at narrowed level in subgroups with varying degrees of severity of clinical symptoms

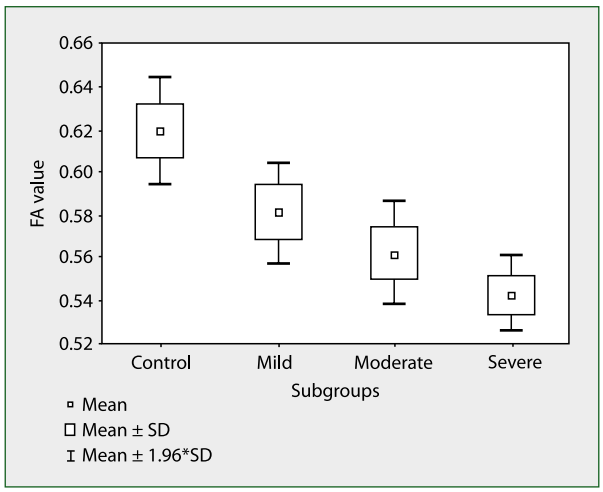

Figure 4. Mean FA values at narrowed level in subgroups with varying degrees of severity of clinical symptoms

Discussion

The choice of treatment for CSM (surgical *vs.* conservative) is still controversial. On the one hand, we have physiotherapists, neurologists and anaesthetists involved in treatment at pain clinics who conduct non-surgical treatments such as physical therapy, immobilisation with orthotics, medications, and spinal injections. On the other hand, there are orthopaedic surgeons and neurosurgeons performing spinal decompression surgery with anterior or posterior stabilisation anteriorly or posteriorly [28, 29]. Some studies have suggested that surgical treatment may be more advantageous than non-operative treatment [30, 31]. Patients in this group have shown improvements in pain and functional status, whereas patients who were managed non-operatively were able to perform fewer activities of daily living and had progressive worsening of neurological symptoms [29]. Another study by Bond et al. [32] showed that patients treated surgically for mild cervical myelopathy did not differ from those treated conservatively with respect to baseline radiographic and demographic parameters.

Given the lack of appropriate treatment evidence, there is a need to identify patients in early stage CSM who are more likely to respond to adequate treatment. Therefore, DTI assessment can be very useful, both for clinicians in deciding on the optimal treatment, as well as for the patient's consent for surgery. Although serious operative complications are rare, the risk may still be unacceptable for someone with non-progressive mild symptomatology [33].

The aim of this study was to demonstrate changes in the spinal cord that are invisible to the human eye in a standard MRI scan in patients with clinical signs of myelopathy. According to our observations, the spinal cord signal in the healthy control group, and in patients, was normal, even at the location at the narrowed level of stenosis. However, the ADC values were significantly higher, and the FA values were significantly lower, in patients compared to the healthy control subjects.

A major advantage of our study is the direct comparison of changes in the core at the same level in both the test and control groups. Different sections of the core differ in the volume of grey and white matter, which may affect the final results. Apart from our study, only two research teams have approached the above problem in the same way.

However, in contrast to our study groups, in previous studies the numbers of patients have been very small. Ying et al. [25] separated from their study group (consisting of 32 people) a group of 15 people without changes in the spinal cord signal and compared them to a control group of 21 people. In their study, at the location of the highest degree of cord compression, a statistically significant increase in the ADC value and a decrease in the FA value were demonstrated between the group without the altered core signal and the control group. In the second study, 12 patients with clinical symptoms of myelopathy without changes in the spinal cord were compared in an MRI study with a group of 40 people without clinical symptoms [26]. A statistically significant increase in the ADC value was demonstrated in these individuals.

Changes in DTI parameters indicate microstructural disorder of the core that is not normally visible in MRI studies. These changes are the result of pressure on the core and are indicative of damage. A decrease in the FA value may reflect the degree of microstructural disorganisation within the spinal cord, suggesting an extension of the extracellular space, in the case of vasogenic oedema, or a reduction in the amount of fibre within the extracellular space [34]. The increase in the ADC value indicates that the movement of molecules is freer, which indicates damage to cell membranes.

Interesting observations by Wen et al. [3] stated that patients with cervical myelopathy symptoms showed changes not only in the location of the most severe stenosis, but also in places distal to this level. This conclusion was based on DTI measurements from the C2/C3 level in patients with clinical signs of cervical myelopathy and corresponding levels in the group without clinical symptoms, showing significantly lower FA values and increased ADC values in patients. Our results, similar to other available studies [24, 35–37], concur with the observations made by Wen et al. We did not show a statistically significant difference in DTI values between patients with clinical symptoms of myelopathy and healthy controls at the C2/C3 level. In one study, Kara et al. [37] performed MRI on 16 patients with clinical symptoms of cervical myelopathy, in whom the cervical spine had a normal signal in T2-weighted images. They found an increase in ADC values and a decrease in FA values at the level of the greatest compression on the spinal cord compared to the uncompressed C2/C3 level in these patients. The methodology of Kara et al.'s [37] study was very close to that of our work, although the group of patients was small (only 16 patients). Similar results were presented by Toktas et al. [38] in 21 patients who also showed an increase in ADC and a decrease in FA in segments affected by stenosis compared to the C2/C3 level.

It should be emphasised that in our work at the C2/C3 level, no degenerative changes or spinal cord compression were found. It would seem therefore reasonable to standardise DTI by referring to FA and ADC values at the level of the greatest degree of stenosis to the unchanged diseased (normal) C2/ /C3 level.

Although many reports have shown that FA values gradually decrease as it approaches the lower level, results from five reports [19, 25, 27, 39, 40] show that despite the decreasing tendency of FA values along the cord, no significant statistical differences in FA values is seen. Moreover, in our work at the C2/C3 level, no degenerative changes or spinal cord compression were found. It seems therefore reasonable to standardise DTI by referring to FA and ADC values at the level of the greatest degree of stenosis to the unchanged diseased (normal) C2/C3 level.

The reasons for the lowering of the FA value are not entirely clear, but it is believed that the decrease in the FA value may be affected by the anatomical structure of the cord, and in particular the fact that in its lower part the ratio of white to grey matter volume increases. Some reports comparing separately calculated DTI parameters for white matter and grey matter have shown that in healthy subjects FA values were higher in white matter than in grey matter due to greater white matter anisotropy [41–44].

Another aim of our study was to determine whether the severity of cervical myelopathy symptoms correlates with the change in FA and ADC values. The JOA scale was used to assess the severity of cervical myelopathy. We presented a correlation between individual points of the JOA scale and DTI values, showing a negative correlation between the ADC value at the site of the most severe stenosis, plus a positive correlation between the FA value at the site of the most severe stenosis, and the JOA scale. There have been many studies showing a strong positive correlation between the JOA scale and FA values in patients with visible signal changes. Most of them have confirmed our observations.

A few researchers have described a positive correlation between FA values and the JOA score, but shown no correlation between the ADC value and the JOA score [21, 27, 45]. We also indicate that the ADC value at the site of the most severe stenosis increases with increasing severity of symptoms, while the FA value decreases. These results have also been confirmed by other authors [3, 21, 26, 45]. A report showing no relationship between DTI and the severity of myelopathy was presented by Lee et al. [13], in which 20 patients on the basis of the JOA scale were divided into two equal groups: a 'neurologically better' group above 11 points and a 'neurologically worse' group below 10 points. The authors did not record a statistically significant difference in the DTI parameters between the two groups, which may be related to the small number of groups or to an overly generalised division into groups.

To the best of our knowledge, we are the first to demonstrate a correlation between clinical symptoms in patients without any changes in the core signal with DTI values measured in the entire spinal cord.

This work has its limitations. One was the use of a questionnaire to assess the severity of clinical symptoms reported by patients. Such an approach is widely accepted in patients with myelopathy. Nevertheless, every patient experiences pain to a different degree and interprets their clinical symptoms differently. Another limitation of the work was a lower ratio of women to men (2:1) in the studied group, i.e. 86 (67.2%) *vs.* 42 (32.8%), than in the control group, i.e. 24 (64.9%) *vs.* 13 (35.1%). The final limitation of the study was the fact that the control group consisted of people without clinical symptoms, but in half of the cases we observed degenerative changes. This is, however, both a disadvantage and an advantage of the work in that it allowed us to conclude that not all degenerative changes lead to clinical symptoms.

The advantages of this work were: the use of a non-invasive imaging technique, a large group of 128 people, a homogeneous group of patients with cervical myelopathy caused by degenerative disease with no MR signal changes, and the

possibility of performing repeated examinations which allowed us to monitor patients with cervical myelopathy during their treatment.

Conclusions and clinical implications

Diffusion tensor imagining can be used to assess patients with cervical myelopathy symptoms, and is a more sensitive method than morphological MRI examination. Changes that are not visible on a structural MRI scan are visible in the basic DTI parameters at the site of the most severe stenosis, indicating disruption of the core microstructure. DTI values measured in the entire spinal cord correlated with the severity of clinical symptoms.

Extending standard MRI to include assessment of AF and ADC may be helpful in deciding treatment modalities (conservative *vs.* surgical) for patients with visible canal stenosis without full neurological symptoms. It may be useful to select patients for urgent rehabilitative treatment. It may also be useful for physicians evaluating the degree of health impairment in patients after spinal injury.

This study is a starting point for further research, e.g. evaluating the extent of AF and ADC lesion withdrawal after surgical treatment.

Conflicts of interest: *None*

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