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Research article

Cervical spondylotic myelopathy: Changes of fractional anisotropy in the spinal cord and magnetic resonance spectroscopy of the primary motor cortex in relation to clinical symptoms and their duration

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ABSTRACT

Objective: To determine the changes in fractional anisotropy (FA) at the proximal spinal cord and in magnetic resonance spectroscopy (MRS) of the precentral gyrus in patients with cervical spondylotic myelopathy (CSM) with respect to clinical symptoms and their duration.

Material and Methods: 20 patients with CSM (7 female; mean age 64.6 ± 10.5 years) and 18 age/sex matched healthy controls (9 female; mean age 63.5 ± 6.6 years) were prospectively included. Clinical data (modified Japanese Orthopaedic Association Score (mJOA) and Neck Disability Index (NDI)) and 3T MR measurements including DTI at the spinal cord (level C2/3) with FA and MRS of the left and right precentral gyrus were taken. Clinical correlations and regression analyses were performed.

Results: Mean clinical scores of patients were significantly different to controls (mJOA; CSM: 10.2 ± 2.9; controls: 18.0 ± 0.0, $p < 0.001$; NDI; CSM: 41.4 ± 23.5; controls: 4.4 ± 6.6, $p < 0.001$); FA was significantly lower in patients (CSM: 0.645 ± 0.067; controls: 0.699 ± 0.037, $p = 0.005$). MRS showed significantly lower metabolite concentrations between both groups: creatine (Cr) (CSM: 46.46 ± 7.64; controls: 51.36 ± 5.76, $p = 0.03$) and N-acetylaspartate (NAA) (CSM: 93.94 ± 19.22; controls: 107.24 ± 20.20, $p = 0.05$). Duration of symptoms ≤6 months was associated with increased myo-inositol (Ins) (61.58 ± 17.76; 44.44 ± 10.79; $p = 0.02$) and Ins/Cr ratio (1.36 ± 0.47; 0.96 ± 0.18; $p = 0.014$) compared to symptoms > 6 months.

Conclusion: Metabolic profiles of the precentral gyrus and FA in the uppermost spinal cord differ significantly between patients and healthy controls. Ins, thought to be a marker of endogenous neuroinflammatory response, is high in the early course of CSM and normalizes over time.

1. Introduction

Chronic spinal cord injury caused by degenerative narrowing of the cervical spine is the most frequent cause of tetraparesis, especially if left untreated (Fig. 1) [1]. Cervical spondylotic myelopathy (CSM) is a prevalent neurosurgical disease with an incidence that is expected to rise even further due to the aging world population [2]. The presumed pathological biomechanics of CSM are continuous compression and repetitive microtraumas, resulting in chronic spinal cord injury [3]. Decompressive surgery is the only known effective treatment. However,

Abbreviations: ANOVA, analysis of variance; Cho, choline; Cr, creatine; CSF, cerebrospinal fluid; CSM, cervical spondylotic myelopathy; DTI, diffusion tensor imaging; EPI, echo-planar imaging; FA, fractional anisotropy; fMRI, functional MRI; Ins, myo-inositol; mJOA, modified Japanese Orthopaedic Association-Score; MRS, magnetic resonance spectroscopy; MANOVA, multivariate analysis of variance; NAA, *N*-acetylaspartate; NDI, Neck Disability Index; T1w, T1-weighted; T2w, T2-weighted

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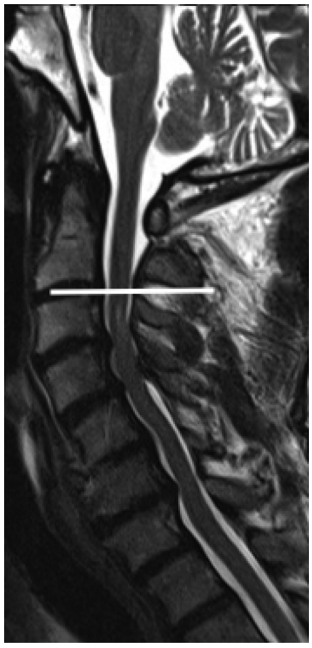

Fig. 1. Sagittal T2w image of the cervical spine in a patient with high-grade multi-segmental stenosis at C3/4, C4/5 with associated pathological signal increase of the spinal cord at C3/4. Line of reference at C2/3 for diffusion tensor imaging (DTI) and measurement of fractional anisotropy (FA).

postsurgical results vary: The majority of patients improve clinically or stabilize postoperatively, whereas some patients worsen secondarily even after sufficient decompression was achieved [4–6]. As the reasons for this remain unclear, further understanding of the underlying pathophysiology is needed. Magnetic resonance imaging (MRI) is the standard method for visualizing the anatomy for surgical decision making. However, the degree of stenosis and particularly the pathological T2w signal increase of the spinal cord are only weak indicators of neuronal impairment and do not correlate well with disease severity or duration [7]. Recent studies suggest that MR parameters at cellular and molecular level, namely diffusion tensor imaging (DTI) and related parameters as well as magnetic resonance spectroscopy (MRS), track the underlying pathology more closely [8–10]. FA (fractional anisotropy) derived from DTI can measure the degree of non-random arrangement of tracks in the spinal cord. It is well known that FA is decreased in patients with CSM and may correlate negatively with severity of CSM [10–14]. MRS allows non-invasive measurement of certain neuronal metabolites. However, the alterations of metabolism are more complex and a variety of changes in MRS have been described; yet no such correlation was found.

This study was set out to investigate the derangement of fiber tracts at the spinal cord as well as the metabolic profile of the primary motor cortex in patients with CSM. Of particular interest was how FA relates to changes in MRS within the same cohort at a single point in time. These two measurements have not previously been investigated simultaneously in CSM. The second focus was to examine the correlation of these parameters with the presenting clinical findings of patients with CSM with the goal to better understand the pathomechanism and to identify markers with clinical implication.

2. Materials and methods

2.1. Subjects

Twenty patients (13 male, 7 female; mean age 64.6 ± 10.5 years; 15 right-handed) (Table 1) with CSM and an indication for surgical decompression were prospectively included and underwent MR examinations (including MRS and DTI) as well as clinical examinations. Exclusion criteria were neurological disorders other than cervical myelopathy: neurodegenerative disease, cerebral stroke, cerebral hemorrhage or spinal trauma. The control group consists of healthy volunteers without neurological disease or neurological deficit in their medical history and underwent identical examinations. The control group consisted of 18 participants (9 male, 9 female; mean age 63.5 ± 6.6 years; 13 right-handed). Clinical neurological examination and functional neurological status were assessed by modified Japanese Orthopaedic Association Score (mJOA) (normal function: 18 points; mild myelopathy/grade 1: 15–17 points; moderate myelopathy/grade 2: 12–14 points; severe myelopathy/grade 3: 0–11 points) [15] and Neck Disability Index (NDI) [16]. All individuals included in the study gave written informed consent in compliance with the Declaration of Helsinki (Medical Association 2008). The study was approved by the local ethics committee of the Medical Faculty (EK 164/13).

2.2. Magnetic resonance examinations

MRI was performed on a 3 T scanner (Magnetom Prisma; Siemens, Erlangen, Germany) with a 20-channel head/neck coil and lasted 45–50 min.

The following routine sequences of the cervical spine were acquired: sagittal T1-weighted (T1w) and T2-weighted (T2w) as well as axial T2w fast spin-echo sequences of the stenotic segments. DTI was performed at the proximal spinal cord (C2/3) (Figs. 1 and 2). This site was chosen because measurements taken cranial to the culprit lesion without spinal stenosis render more reliable values and correlate best with clinical status [13]. A multi-shot spin-echo echo-planar imaging (EPI) sequence (RESOLVE, Siemens, Erlangen, Germany) with readout-segmented EPI and parallel imaging (GRAPPA with acceleration factor of 2 and 24 reference lines) to decrease susceptibility was used [17]: repetition time/echo time, 2500/72 ms; field of view, 165 x 50 mm; flip angle: 180°; 20 diffusion encoding directions; b value: 800 s/mm^2; slice thickness: 5 mm; phase encoding direction: anterior to posterior; resolution of acquisition: 0.6 × 0.6 x 5.0 mm. Pulse triggering was used to avoid artefacts from cerebrospinal fluid (CSF) pulsation. FA maps were generated on the scanner. For quantitative image analysis, regions of interest, comprising the entire cross section of the spinal cord, were drawn by a single radiologist with 5 years of experience and mean FA values were calculated (Fig. 2).

Consistent voxel placement of the MRS at the hand representation area ("hand knob") of the precentral gyrus (Fig. 3) on both hemispheres was achieved via anatomical images and functional MRI (fMRI) [18]. The following anatomical sequences of the brain were acquired to aid voxel placement: axial and coronal T1w fast spin-echo sequences and sagittal T1w (inversion-prepared three-dimensional magnetization-prepared rapid acquisition gradient-echo sequences/MPRAGE). The activation paradigm for axial fMRI was repeating finger to thumb opposition in 7 cycles lasting 30 s each. Patients were trained accordingly before the examination and cues were given acoustically during the exam. MRS was performed via single voxel spectroscopy using point-resolved spin-echo sequence (PRESS) (repetition time/echo time, 2000/30 ms; flip angle, 90°; averaging, 80; voxel size, 20 × 20 x 20 mm). Saturation was performed before each MRS around the voxel to suppress signal contamination from nearby structures. Automated shimming with manual adjustments whenever needed was performed via linear and Z^2 shims to ensure a full width at half maximum (FWHM) below 15 Hz. Raw data were analyzed using the scanner's spectroscopy analysis (syngo MR, Siemens, Erlangen, Germany). Analysis was performed in the frequency domain and peak integrals were calculated as arbitrary units for major neuronal metabolites: choline (Cho), creatine (Cr), hydrated creatine (Cr2), myo-inositol (Ins) and N-acetylaspartate (NAA). Furthermore, ratios of the metabolites were calculated and included in the subsequent analyses.

Table 1
Sample characteristics, clinical data, fractional anisotropy and MR spectroscopy means, standard deviations and group comparisons.

Variable	CSM_{total}(n = 20)	$CSM_{\leq 6month}$(n = 6)	$CSM_{>6month}$(n = 14)	Controls (n = 18)	CSM_{total} vs. Controls	*p*	$CSM_{\leq 6m}$vs.$CSM_{>6m}$	*p*
Sample characteristics								
CSM duration (month) [*M* (*SD*)]	16.7 (14.7)	4 (2.1)	22.1 (14.4)	–	–	–	t = -3.03	**0.007**
age [*M* (*SD*)]	64.6 (10.5)	63 (10.0)	65.3 (11.0)	63.5 (6.6)	t = -0.38	0.71	t = -0.44	0.67
male [N(%)]	13 (65.0)	4 (66.7)	9 (64.3)	9 (50.0)	χ^2 = 0.87	0.35	χ^2 = 0.01	0.91
right handed [N(%)]	15 (75.0)	5 (83.3)	10 (71.4)	13 (72.0)	χ^2 = 0.04	0.85	χ^2 = 0.32	0.57
Clinical data								
mJOA [*M* (*SD*)]	10.2 (2.9)	11.3 (2.1)	9.6 (3.1)	18 (0.0)	F = 132.6	**0.000**	F = 1.47	0.24
NDI [*M* (*SD*)]	41.4 (23.5)	33.0 (17.3)	45.2 (25.6)	4.4 (6.6)	F = 41.16	**0.000**	F = 1.12	0.31
Diffusion tensor imaging								
FA [*M* (*SD*)]	0.645 (0.670)	0.647 (0.039)	0.644 (0.078)	0.699 (0.037)	F = 8.9	**0.005**	F = 0.007	0.94
MR spectroscopy								
Cr2 [*M* (*SD*)]	70.45 (18.55)	81.12 (21.27)	65.52 (12.64)	69.97 (10.01)	F = 0.01	0.92	F = 3.27	0.09
Ins [*M* (*SD*)]	49.86 (15.24)	61.58 (17.76)	44.44 (10.79)	49.71 (16.92)	F = 0.00	0.98	F = 6.90	**0.02**
Cho [*M* (*SD*)]	38.67 (11.52)	42.10 (16.77)	37.07 (8.56)	41.04 (11.02)	F = 0.41	0.52	F = 0.77	0.39
Cr [*M* (*SD*)]	46.46 (7.64)	46.43 (9.90)	46.47 (6.84)	51.63 (5.76)	F = 5.4	**0.03**	F = 0.000	0.99
NAA [*M* (*SD*)]	93.94 (19.22)	86.63 (17.61)	97.32 (19.64)	107.24 (20.20)	F = 4.2	**0.05**	F = 1.29	0.27
NAA/Cr [*M* (*SD*)]	2.03 (.32)	1.89 (.30)	2.10 (0.32)	2.08 (0.34)	F = 0.17	0.69	F = 1.93	0.18
Ins/Cr [*M* (*SD*)]	1.08 (.35)	1.36 (0.47)	0.96 (0.18)	0.98 (0.38)	F = 0.81	0.38	F = 7.56	**0.014**

Cho = choline; Cr = creatinine; Cr2 = hydrated creatinine; CSM = cervical spondylotic myelopathy; FA = fractional anisotropy; Ins = myo-inositol; mJOA = modified Japanese Orthopaedic Association Score; NAA = N-acetylaspartate; NDI = Neck Disability Index.
[a] *p*-values < 0.05 were considered to be statistically significant.

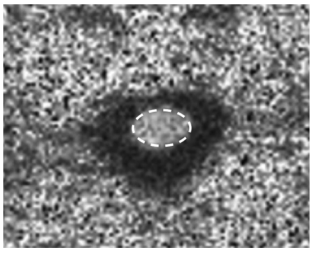

Fig. 2. Map of fractional anisotropy (FA) of the proximal spinal cord (level C2/3) with region of interest comprising the entire spinal cord.

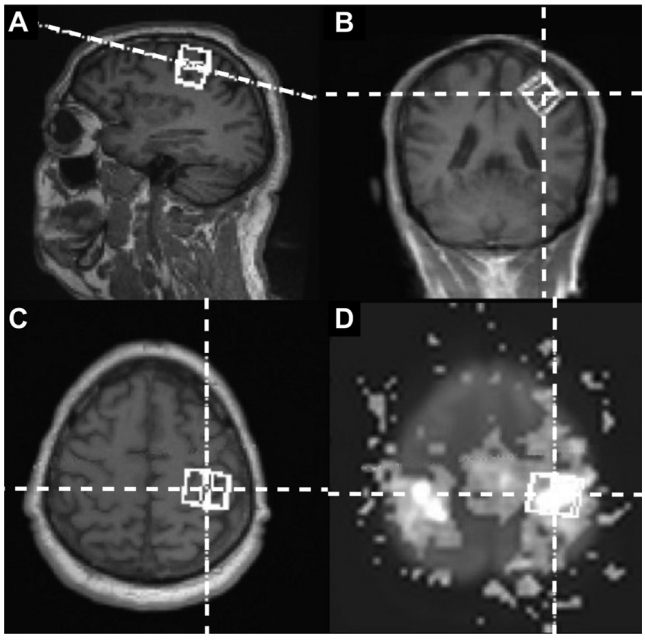

Fig. 3. MR images utilized for placement of voxel at the primary motor cortex for magnetic resonance spectroscopy (MRS): sagittal (A), coronal (B) and axial T1w images (C), axial t-map of functional MRI (fMRI) with highest signal at the hand representation area "hand knob" (D).

2.3. Statistical analysis

For statistical analysis, IBM SPSS Statistics Version 25 (IBM Corporation, Armonk, NY) was used. To assess whether the samples match according to age, gender and handedness, an independent samples *t*-test (to compare age) and two Chi^2-tests (to compare gender and handedness between patients and the control group) were conducted. Independent samples *t*-tests, Chi^2, one-way analysis of variance (ANOVA) and multivariate analysis of variance (MANOVA), Pearson correlation and linear regression analysis were conducted for statistical analysis (*p*-values < 0.05 were considered to be statistically significant). Group means and standard deviations as well as statistical significances are presented in Tables 1–3.

A one-way ANOVA between subjects (CSM-vs. control group) was used to analyze the effect of CSM on the clinical output scores (mJOA, NDI). Next, a one-way MANOVA with Bonferroni correction was conducted to test for differences in FA and the metabolites (Cr, Cr2, Ins, Cho, NAA, NAA/Cr, Ins/Cr) between the groups (CSM, controls). Furthermore, post-hoc analyses were performed to examine mean difference comparisons between groups and all dependent variables. Effect sizes as estimated by partial η^2 will be reported for the significant results (0.01 = small, 0.06 = medium and 0.14 = large effect). Additionally, a one-way ANOVA between subjects ($CSM_{\leq 6\ months}$ vs. $CSM_{>6\ months}$) was used to analyze the effect of duration of CSM on the clinical output scores (mJOA, NDI). Finally, to further examine the relation between the duration of CSM in the total patient sample and the outcome parameters, Pearson's *r* correlation analyses were performed and results are reported on a significance level of $p < 0.05$ (2-sided). According to Cohen's guidelines, Pearson's correlations of $r = 0.1$ represent a small, $r = 0.3$ a medium, and $r = 0.5$ a large effect. A hierarchical regression analysis was calculated to test whether the clinical variables and the derived significant metabolite correlates predict the duration symptoms of CSM had been present. With the hierarchical approach the incremental predictive power of the (competing) predictors was determined: one for the clinical variables referring to the functional neurological status (mJOA and NDI) and the other for the significant metabolite (Ins).

Table 2
Correlations between duration of CSM (≤ 6 month; > 6 month) and FA, metabolites and ratios.

		FA	Cr2	Ins	Cho	Cr	NAA	NAA/Cr	Ins/Cr
duration	Pearson's *r*	−0.17	−0.39	**−0.53**[a]	−0.31	0.001	0.17	0.21	**−0.51**[a]
	Sig. (2-tailed)	0.49	0.09	**0.02**	0.19	0.998	0.47	0.37	**0.02**
	N	19	20	20	20	20	20	20	20

Cho = choline; Cr = creatinine; Cr2 = hydrated creatinine; CSM = cervical spondylotic myelopathy; FA = fractional anisotropy; Ins = myo-inositol; NAA = N-acetylaspartate.
p-values < 0.05 were considered to be statistically significant.
[a] Correlation is significant at the 0.05 level (2-tailed).

Table 3
Hierarchical linear regression analysis predicting Chronicity of CSM.

CSM duration	Model 1			Model 2		
	Stand. Beta	T	*p*	Stand. Beta	t	*p*
mJOA	−0.17	−0.54	0.60	−0.27	−1.11	**0.28**
NDI	0.37	1.19	0.25	−0.30	1.23	0.24
Ins	–	–	–	−0.57	−3.31	**0.01**
Model	**F(216) = 2.65; *p* = 0.10**			**F(315) = 6.53; *p* < 0.01**		
R^2	**0.25**			**0.57**		
Adj. R^2	**0.16**			**0.48**		
Change in R^2	**0.25, *p* = 0.10**			**0.32, *p* < *0.01***		

CSM = cervical spondylotic myelopathy; Ins = myoinositol; mJOA = modified Japanese Orthopaedic Association Score; NDI = Neck Disability Index.
p-values < 0.05 were considered to be statistically significant.

3. Results

3.1. Patients and control group

No significant differences in age (patients: mean 64.5 ± 10.5, median 63.5, range 42–82; controls: mean 63.5 ± 6.6, median 64, range 48–74) (t(36) = -0.38, p = 0.71), gender and handedness were noted between patient and controls (gender: $\chi^2 = 0.87$, p = 0.35; handedness: $\chi^2 = 0.04$, p = 0.85). The ANOVA showed clear differences between the groups regarding mJOA (CSM: 10.2 ± 2.9; controls: 18.0 ± 0.0; F(1, 36) = 132.6, p < 0.001) and NDI scores (CSM: 41.4 ± 23.5; controls: 4.4 ± 6.6; F(1, 35) = 41.16, p < 0.001) (Table 1).

3.2. MRI

All 20 patients presented with severe cervical stenosis with the level of maximal stenosis between C 3/4 and C 6/7 (C3/4: n = 5; C4/5: n = 6; C5/6: n = 7; C6/7: n = 2) – no significant stenosis was present at or above C2/3. Pathological T2w signal increase of the cervical spinal cord was appreciable in 18/20 patients.

3.3. FA and MRS

No significant difference in the concentration of metabolites between the left and right hemisphere was noted in the one-way ANOVA. Therefore, pooled data were used for further analyses (Table 1) as in the work of Kowalczyk et al. [9].

The MANOVA on group differences in FA, metabolite concentration (Cr, Cr2, Ins, Cho, NAA) and their ratios (NAA/Cr, Ins/Cr) showed significant differences (F(2, 28) = 2.71, p < 0.05, partial $\eta^2 = 0.44$) between patients and controls. Post-hoc comparisons of group differences in FA (F(1, 35) = 8.9, p = 0.005, partial $\eta^2 = 0.20$), Cr (F(1, 35) = 5.4, p = 0.03, partial $\eta^2 = 0.13$) and NAA (F(1, 35) = 4.2, p = 0.05, partial $\eta^2 = 0.11$) were also significant. The patient group showed reduced FA (patients: 0.645 ± 0.067; controls: 0.699 ± 0.037), Cr (patients: 46.46 ± 7.64; controls: 51.36 ± 5.76) and NAA (patients: 93.94 ± 19.22 controls: 107.24 ± 20.20). No significant differences were noted in the other parameters (p > 0.05) (Table 1).

3.4. Subanalysis of CSM patients: $CSM_{\leq 6\ months}$ vs. $CSM_{>6\ months}$ vs. controls

No significant difference in age (CSM ≤ 6 months: 63.0 ± 10.0; CSM > 6 months: 65.3 ± 11.0; t(18) = 0.44; p = 0.67), gender and handedness (gender: $\chi^2 = 0.01$, p = 0.91; handedness: $\chi^2 = 0.32$, p = 0.57) was noted within the patient group. No significant difference in mJOA (CSM ≤ 6 months: 11.3 ± 2.1; CSM > 6 months: 9.6 ± 3.1; F(1, 18) = 1.47, p = 0.24) or NDI scores (CSM ≤ 6 month: 33.0 ± 17.3; CSM > 6 months: 45.2 ± 25.6; F(1, 18) = 1.12, p = 0.31) was noted within the patient group (Table 1).

The MANOVA on the group differences of FA, metabolite concentration (CR, Cr2, Ins, Cho, NAA) and the ratios (NAA/Cr, Ins/Cr) was not significant (F(8, 10) = 1.88, p = 0.17, partial $\eta^2 = 0.6$). However, post-hoc comparisons showed significant group differences in Ins (F(1, 17) = 6.9, p = 0.02, partial $\eta^2 = 0.29$) and in Ins/Cr ratio (F(1, 17) = 7.56, p = 0.014, partial $\eta^2 = 0.31$). Patients with shorter duration of symptoms (≤ 6 months) showed increased Ins (CSM ≤ 6 months: 61.58 ± 17.76; CSM > 6 months: 44.44 ± 10.79, *p* = 0.02) and Ins/Cr ratio (CSM ≤ 6 months: 1.36 ± 0.47; CSM > 6 months: 0.96 ± 0.18, *p* = 0.014). Likewise, the ratio of Ins/Cr was significantly different between patients with shorter duration of symptoms when compared to healthy controls (CSM ≤ 6 months: 1.36 ± 0.47; controls: 0.98 ± 0.38, *p* = 0.02). All other parameters did not differ significantly within the patient group (Table 1).

3.5. Symptom duration in correlation to MRS and FA

The only significant associations between the duration of CSM in the total patient sample and the outcome parameters were found between the duration of CSM and Ins (r = −0.53, p = 0.02) and between the duration of CSM and the Ins/Cr ratio (r = −0.51, p = 0.02) (Table 2). All other variables were not associated with the duration of CSM.

3.6. Prediction of chronicity of CSM through mJOA, NDI and Ins

In order to test how far the significant associations found in our correlation analysis are predictive of how long symptoms of CSM had been present, a hierarchical regression analysis was used. The results are presented in Table 3. In Model 1 mJOA and NDI were entered as predictors; in Model 2 the metabolite Ins was added as a parameter. Only Model 2 reached significance. mJOA and NDI values alone were not predictive for the period symptoms had been present. Adding Ins in Model 2 showed that Ins is significantly associated with the duration symptoms had been present in CSM. Model 2 explains 57% of variance of which 32% are explained by Ins alone.

4. Discussion

Degenerative changes in CSM with spinal cord compression result in

microstructural damage of the spinal cord, which can be measured with DTI [10,19]. In our study we found clear differences in DTI with a decrease of FA in patients compared to controls. In former studies also correlations between CSM severity (mJOA) and degree of DTI abnormalities could be demonstrated [10–14]. Even though Jones et al. report the best correlation of FA to clinical symptoms at the exact site of our measurement in the proximal spinal cord (C2/3) and Budzik et al. reached significance at this level [11,13], no such correlation could be demonstrated in our study. A reason for this might be that only a single segment in the proximal spinal cord was considered, although these studies suggest even more reliable values cranial to the culprit lesion, as the proximal spinal cord has a larger cross section and therefore is less susceptible to artefacts than at the stenotic segments. Another factor might be the small number of CSM patients in each subgroup with respect to severity grade as in the study of Lee et al. with similar findings [20].

To our knowledge, we are the first to measure MRS at the precentral gyrus and FA at the cervical spine in the same patients. Although MRS and FA measurements differed significantly between patients and healthy controls, we did not find a significant correlation between these measurements within the groups. We believe that changes in metabolic profile are more dependent on the degree of functional abnormality and its duration. Therefore, as FA is a marker of microstructural integrity, these changes only indirectly depend on the underlying structural abnormality itself.

NAA is an abundant neurotransmitter found exclusively in neurons [7]. A decrease in NAA concentration indicates an impairment of neuronal function [21], reflecting mitochondrial dysfunction and decreased neuronal density [8,22,23]. The significant decrease of NAA in our cohort with a tendency of even lower NAA in patients with shorter symptoms supports previous findings on metabolic changes in the precentral gyrus [9], which are consistent with a loss of neuronal integrity in CSM [8].

Cr is a central molecule in metabolism, which is found in particularly high concentrations in tissues with high energy requirements, e.g. the central nervous system. A malfunction or decrease of the Cr system is thought to be responsible for many age-related neurodegenerative diseases [24] and mental retardation [25]. The significantly reduced concentration of Cr at the precentral gyrus in CSM patients seems to be a sign of impaired neuronal function resulting in reduced metabolic activity.

In contrast to other studies, we could not demonstrate a significant decrease of NAA/Cr ratio in patients with CSM compared to healthy controls [9,26]. Similarly, patients examined by Aleksanderek et al. did not show any significant differences when compared to healthy controls [8]. An explanation for our contrasting finding of significantly decreased NAA and Cr not yet described in the literature may lie in the relatively long duration of symptoms had been present in our patient cohort (mean 16.7 months) compared to Aleksanderek et al.: ≤ 1 year; Kowalczyk et al.: < 1 year; Holly: not specified [8,9,26].

Consistent with the hypothesis of reduced metabolite abnormalities with prolonged symptoms, Ins and Ins/Cr were significantly lower in patients with longer symptom duration (> 6 months) when compared to patients with shorter duration of symptoms, underlining that acute inflammatory changes have subsided in the chronic state. Ins is thought to be a marker of glial mass with differing levels in different diseases [9]. Altered levels are observed in Alzheimer's disease, multiple sclerosis [27–30], major depressive disorder and hepatic encephalopathy [31,32]. In the current literature on CSM no significant changes of Ins in the precentral gyrus have yet been reported [9,33]. However, in our statistical regression model Ins predicted the duration symptoms of CSM had been present more precisely than mJOA. The relatively high concentration of Ins in patients with shorter symptom duration (≤ 6 months) in our study can be explained by reactive gliosis accompanying subacute neuroinflammation [34]. Endogenous inflammatory reactions in the spinal cord in CSM have been detected and reported on in previous studies [35,36]. In our study we were able to demonstrate increased inflammatory changes in the precentral gyrus of patients in the early state of CSM. A hypothesis for these findings could be the affection of the entire motor tract, starting in the spinal cord, which is triggered by the stenosis, and is spreading retrogradely and affecting the primary motor cortex. The increased values of Ins and Ins/Cr compared to patients with longer duration of symptoms as well as Ins/Cr to healthy controls support this theory. The significantly lower concentration of Ins in chronic cases is consistent with a chronic state where inflammation has subsided, potentially accompanied by a decrease in glial mass. Since the concentration of Cr is practically constant in our patient cohort, the significantly decreased Ins/Cr ratio can be solely attributed to the changes in Ins.

The following limitations should be acknowledged. In analysis of FA the voxels considered comprised the entire cross section of the spinal cord and did not account for grey and white matter. As the vast majority of the spinal cord is made up of fiber tracts with only relatively scarce grey matter the error introduced by this is most probably negligible. The chosen slice thickness of 5 mm is relatively large. However, resolution along the long axis of the patient is of much lesser concern in the spinal cord where spinal tracts are mostly oriented parallel, than it would be in the brain. In our study, as in prior works, the metabolic profile of the precentral gyrus was considered to be constant at a given point in time, disregarding the state of activity [8,9,26,33]. However, since the time of measurement in relation to the finger tap paradigm was constant, systematic error could be avoided. Due to the modest sample size only three patients with mild myelopathy could be included; ultimately subgroup analyses were not possible for this group. The surgical benefit in CSM patients was not yet determined with respect to clinical outcome, changes in FA or metabolic profile, as they are subject to an ongoing investigation.

5. Conclusion

Measurements of FA in the spinal cord at the level C2/3, above the stenotic areas and MRS in the primary motor cortex showed significant differences between patients with CSM and healthy controls. However, there was no correlation between the results of these two methods.

FA was lower in patients, but did not correlate with clinical symptoms. We observed an increase in Ins in patients with a shorter history of CSM. In them, Ins may be a marker of endogenous neuroinflammatory response secondarily normalizing in the chronic state of CSM. Further studies assessing the impact particularly on postsurgical outcome are a topic of ongoing research.

Conflict of interest statement

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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