Remote motor system metabolic profile and surgery outcome in cervical spondylotic myelopathy

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OBJECTIVE In patients with cervical spondylotic myelopathy (CSM), the motor system may undergo progressive functional/structural changes rostral to the lesion, and these changes may be associated with clinical disability. The extent to which these changes have a prognostic value in the clinical recovery after surgical treatment is not yet known. In this study, magnetic resonance spectroscopy (MRS) was used to test 2 primary hypotheses. 1) Based on evidence of corticospinal and spinocerebellar, rubro-, or reticulospinal tract degeneration/dysfunction during chronic spinal cord compression, the authors hypothesized that the metabolic profile of the primary motor cortices (M1s) and cerebellum, respectively, would be altered in patients with CSM, and these alterations would be associated with the extent of the neurological disabilities. 2) Considering that damage and/or plasticity in the remote motor system may contribute to clinical recovery, they hypothesized that M1 and cerebellar metabolic profiles would predict, at least in part, surgical outcome.

METHODS The metabolic profile, consisting of *N*-acetylaspartate (NAA; marker of neuronal integrity), myo-inositol (glial marker), choline (cell membrane synthesis and turnover), and glutamate-glutamine (glutamatergic system), of the M1 hand/arm territory in each hemisphere and the cerebellum vermis was investigated prior to surgery in 21 patients exhibiting weakness of the upper extremities and/or gait abnormalities. Age- and sex-matched controls (*n* = 16) were also evaluated to estimate the pre-CSM metabolic profile of these areas. Correlation and regression analyses were performed between preoperative metabolite levels and clinical status 6 months after surgery.

RESULTS Relative to controls, patients exhibited significantly higher levels of choline but no difference in the levels of other metabolites across M1s. Cerebellar metabolite levels were indistinguishable from control levels. Certain metabolites—myo-inositol and choline across M1s, NAA and glutamate-glutamine in the left M1, and myo-inositol and glutamate-glutamine in the cerebellum—were significantly associated with postoperative clinical status. These associations were greatly improved by including preoperative clinical metrics into the models. Likewise, these models improved the predictive value of preoperative clinical metrics alone.

CONCLUSIONS These preliminary findings demonstrate relationships between the preoperative metabolic profiles of two remote motor areas and surgical outcome in CSM patients. Including preoperative clinical metrics in the models significantly strengthened the predictive value. Although further studies are needed, this investigation provides an important starting point to understand how the changes upstream from the injury may influence the effect of spinal cord decompression.

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KEY WORDS cervical spondylotic myelopathy; ¹H-MRS; remote motor system; neuroinflammation; clinical outcome; spinal decompression surgery

ABBREVIATIONS CSM = cervical spondylotic myelopathy; M1 = primary motor cortex; mJOA = modified Japanese Orthopaedic Association; mJOA-LE = mJOA lower-extremity motor domain; mJOA-UE = mJOA upper-extremity sensorimotor domain; MRS = MR spectroscopy; NAA = *N*-acetylaspartate; SCI = spinal cord injury; ¹H-MRS = proton MRS; 9-HPT = 9-hole peg test.

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CERVICAL spondylotic myelopathy (CSM), the most common degenerative spinal cord disorder in adults older than 55 years,³⁴ is a disabling neurological condition leading to significant impairment of the quality of life. Given the progressive aging of society, the burden of CSM is likely to increase as our population ages.⁴⁶ Although the exact pathophysiology underlying CSM remains uncertain, it is largely accepted to be the results of compressive forces on the spinal cord, likely due to multiple factors.^{34,48,61} In addition to local spinal cord injury (SCI), recent imaging/electrophysiological studies have demonstrated cortical^{16,18,31,66} and cerebellar⁶⁵ abnormalities in these patients. Therefore, the clinical symptoms in CSM are now considered to be the result of both the SCI per se and associated brain plastic changes.

Although spinal decompression surgery is the primary treatment recommended to stop the disease's progression, we have only limited information about why recovery is more limited in some patients than in others.^{22,35} Demographic data, clinical features (see review by Tetreault et al.⁶⁸), metrics of spinal cord damage,^{1,20,32,46,60} and remote sensorimotor system function^{16,18,31,59,64,66} have been explored for predictive value; unfortunately these predictors have not, either in isolation or in combination, provided useful models for health care management or rehabilitation service allocation. Nevertheless, recent findings have indicated that, in addition to SCI itself, damage and/or plasticity in the remote motor system also contributes to functional recovery.^{16,31,57,66} In similar settings, a measure of the cellular/molecular level of such remote changes may add insights into the pathophysiology of CSM, potentially offering informative value for predicting postoperative neurological impairment and recovery in clinical practice.

In the present study, we strove to build understanding of potentially clinically relevant neural biomarkers that might improve prediction of neurological recovery after surgery in CSM patients. We specifically tried to elucidate, for the first time, whether noninvasive measures of the metabolic profile (by using proton MR spectroscopy [¹H-MRS]) of two remote brain areas, primary motor cortex (M1) and cerebellum, predict the extent to which these areas have the reserve to boost activity associated with a reversal of afferent and efferent changes after surgical spinal cord decompression. This study builds upon our prior ¹H-MRS studies in stroke, indicating direct relationships between remote neuron-glia alterations and neurological impairment and recovery,^{9–12} and on a single brain ¹H-MRS study involving CSM patients.³⁸ Specifically, in the latter study, lower levels of a neuronal marker (*N*-acetylaspartate [NAA]⁴⁴) have been found in the affected upper-extremity sensorimotor territory and interpreted as indicating possible neuronal damage or dysfunction at this level. Although these alterations have not demonstrated strong association with clinical status, failing to provide reliable prognostic information, the NAA findings are suggestive of possible cortical metabolic changes associated with CSM.

Here, we address these issues by using ¹H-MRS in a cohort of 21 CSM patients exhibiting upper- and/or lower-extremity neurological deficits. We investigated whether the metabolic profiles (comprising measures of specific metabolites related to neuronal-glial integrity, inflamma-

tion, and status of the glutamatergic system) of each M1 and the cerebellum predict neurological outcome after surgery. We also evaluated metabolite levels in 16 age- and sex-matched controls in order to obtain an estimate of pre-CSM levels in these areas. Based on anatomical evidences of corticospinal tract degeneration in patients with SCI^{28,71} and the M1 spectroscopic observations from CSM patients,³⁸ we hypothesized that the metabolic profile of the hand/arm territory in both M1s would be altered and that these alterations would be associated with the extent of upper-extremity sensorimotor impairment. Likewise, owing to the evidence of spinocerebellar and/or rubro- or reticulospinal tract dysfunction after SCI,^{27,40} we have also hypothesized that the metabolic profile of the cerebellum would be altered and that the alterations would correlate with upper- and/or lower-extremity impairment. In light of our prior stroke studies indicating that ¹H-MRS measures provide insights into brain events that can be informative with respect to achievement of treatment-related gains¹⁰ and that similar neural events are likely to assist brain reorganization following stroke and SCI,^{37,50,57} we expected that ¹H-MRS measures would predict, at least in part, neurological outcome after surgery.

Methods

Participants

Twenty-one patients with clinical symptoms of CSM (mean age [$\pm$ SD] 58.6 $\pm$ 10.6 years, range 42–75 years; 13 males) and 16 age- and sex-matched healthy volunteers (mean age 52.5 $\pm$ 11.4 years, range 38–69 years; 9 males) gave written informed consent according to the Declaration of Helsinki before enrollment. The institutional review board at the Bagdasar-Arseni Hospital (Bucharest) approved this study.

At the time of enrollment, all patients manifested upper-extremity weakness and/or gait abnormalities of no longer than 1 year's duration and had experienced recent clinical deterioration that led to the decision for surgery.

All patients were treated surgically and followed up postoperatively (see below). Imaging studies and clinical assessment were performed prior to surgery in all cases. Imaging included routine cervical spine MRI (to confirm cord compression and exclude other spine pathology; Fig. 1A and Table 1) and ¹H-MRS (see below). Table 1 shows preoperative patient information. Briefly, a total of 6 of 21 patients had 2 levels of spinal cord compression, 10 patients had compression at 3 levels, and 5 exhibited compression at 4 or 5 levels. Patients with more neurological dysfunction appeared to have signal abnormality at the site of compression on T2-weighted MRI. Clinical assessments included 3 valid and highly reliable tests: the modified Japanese Orthopaedic Association (mJOA) scale,⁸ Rolyan 9-hole peg test (9-HPT)¹⁹ (Model A8515, Sammons Preston/Patterson Medical), and a timed 30-m walking test.^{4,51} The mJOA was administered to assess upper-extremity sensorimotor, lower-extremity motor, and sphincter dysfunction (mJOA-total, score of 18 indicating no dysfunction). Because mJOA-total scores alone can be misleading due to the uneven weight placed on each component, we also quantified 2 mJOA subscores:^{42,53,65} one

FIG. 1. **A:** Sagittal T2-weighted MR image obtained in a patient with cervical myelopathy (preoperative mJOA-total score of 11). The white arrow indicates the site of cord compression. A = anterior; P = posterior. **B:** Coronal T2-weighted MR images with spectroscopic voxels placed in the right M1 (left image) and cerebellum (right image). L = left; R = right. **C:** LCMoel spectrum from a voxel located in the right M1 in a healthy control. Signals of *N*-acetylaspartate (NAA), choline (Cho), myo-inositol (mIn), creatine (Cr), and glutamate-glutamine (Glx) are clearly discernable in the spectrum. ppm = parts per million. Figure is available in color online only.

for the upper-extremity sensorimotor domain (mJOA-UE, score of 8 indicating no dysfunction) and one for the lower-extremity motor domain (mJOA-LE, score of 7 indicating no dysfunction). The 9-HPT was administered to assess finger dexterity. To control for unequal disability between the left and right hands, we used the average 9-HPT performance for both hands. To assess the patients' condition when they reached neurological stability after surgery,⁷ clinical testing was repeated 6 months postoperatively.

Patients and healthy controls with a prior history of brain or spinal cord injury, neurological disease, major psychiatric disorder, substance/alcohol abuse or dependence, orthopedic or muscular pathology affecting upper and/or lower extremities, diabetes mellitus, or MRI contraindications were excluded. Notably, the control group underwent cervical MRI (during their participation in a second project, TFR12-EuroSpine), and we found no signs of cervical stenosis in these participants. All participants—patients and controls—were right-handed (based on the Edinburgh Handedness Inventory⁵²).

Preoperative ¹H-MRS Data Acquisition and Analysis

MRI studies were carried out at the Medinst Imaging Center (Bucharest) on a 1.5-T Siemens Magnetom Avanto system within 24 hours after preoperative clinical assessment. Each MRI study included the acquisition of high-resolution T2-weighted MR images (fast spin echo, TR 3200 msec, TE 376 msec, FOV 260 mm, matrix 256 × 256, resolution 1 × 1 × 3 mm³) followed by ¹H-MRS imaging. The total scan duration was approximately 45 minutes.

¹H-MRS Acquisition

Based on anatomical landmarks (<http://neuro.imm.dtu.dk/services/jerne/ninf/voi.html>) identified on T2-weighted MRI, we placed one spectroscopic voxel (15 × 15 × 15 mm³) in the hand territory (the middle genu of the anterior bank of the central sulcus or omega shape structure⁷²) of each M1 and one voxel in the cerebellar vermis (the medial segment of the vermis limited by the paramedian sulci¹³) (Fig. 1B). The hand/arm territory in M1 and the vermis in the cerebellum were selected based on

1) the fact that weakness; numbness of the arms, hands, and/or fingers; and gait dysfunction are the clinical symptoms typically reported in CSM;³⁴ and 2) prior evidence of functional reorganization of these areas during recovery from CSM.^{16,31,59,64,66} The hand territory was specifically selected because it is a well-known area that is easy to recognize on MR images, which should allow for consistency in spectroscopic measurements across subjects. Notably, we used a spectroscopic voxel of 15 × 15 × 15 mm³, which

TABLE 1. Demographic data, preoperative clinical/MRI characteristics, and surgery approach employed in CSM patients

Case No.	Age (yrs), Sex	Stenosis Level	MRI Findings*	Surgical Approach	Preop mJOA-Total Score
1	68, F	C4–7	–	Posterior	17
2	68, M	C4–6	–	Posterior	17
3	58, M	C4–7	–	Posterior	16
4	58, M	C5–7	–	Posterior	15
5	52, M	C4–6	–	Anterior	15
6	65, M	C3–7	–	Posterior	15
7	52, F	C4–6	–	Anterior	15
8	43, M	C4–5	+	Anterior	14
9	42, F	C5–6	–	Anterior	14
10	57, M	C5–6	+	Anterior	14
11	69, M	C4–6	–	Posterior	14
12	65, M	C4–6	–	Posterior	14
13	62, F	C4–5	–	Anterior	14
14	63, F	C4–6	–	Posterior	13
15	50, F	C5–7	+	Anterior	13
16	57, M	C4–6	–	Posterior	12
17	42, F	C5–6	+	Anterior	12
18	63, M	C3–7	+	Posterior	11
19	78, F	C6–7	+	Anterior	11
20	75, M	C4–7	+	Posterior	10
21	44, M	C5–7	+	Posterior	10

* Presence (+) or absence (–) of signal abnormality on spinal MRI.

could not be entirely positioned within the hand territory, so a contribution of surrounding structures, such as arm motor and sensory hand/arm territories, was also present. We minimized the scalp lipid artifact using outer volume suppression bands. ^1H -MRS scans were performed using point-resolved spectroscopy sequence (PRESS) with water suppression (TE 30 msec, TR 1500 msec, averages 220, flip angle 90° , spectral width 1000 Hz). Automated and manual shimming was performed to achieve an optimal full width at half maximum of < 10 Hz of the water signal.^{9,11}

^1H -MRS Analysis

^1H -MRS data were processed by means of LCModel software.⁵⁴ Ratios to a reference metabolite, creatine, which plays an essential role in energy homeostasis and has been shown to give a relatively constant signal in the human brain,⁶² were calculated for 4 metabolites: NAA, myo-inositol (glial marker), choline (cell membrane synthesis and turnover), and glutamate-glutamine (glutamatergic system) (Fig. 1C). These metabolites were selected on the basis of our prior studies and others demonstrating their role in remote reorganization after brain or spinal cord injury.^{9,11,12,26,37}

Based on the evidences of functional/structural changes in the hand/arm territory after SCI^{28,66,71} and the spectroscopic observations from CSM patients,³⁸ we expected to find in M1 lower levels of NAA (reflective of neuronal dysfunction or damage), possible higher levels of myo-inositol (reactive gliosis¹⁵), higher levels of choline (increased cell membrane turnover and breakdown²⁴), and lower levels of glutamate-glutamine (lower activity of glutamatergic system⁶³). Owing to the evidences of spinocerebellar and/or rubrospinal tract dysfunction after SCI,^{27,40} susceptibility of the cerebellum to plastic morphometric changes²⁵ after SCI, and on similarities between SCI and CSM,⁶¹ we have also hypothesized that the metabolic profile of the cerebellum would be altered.

Spinal Decompression Surgery

One neurosurgeon (S.C.C.) performed the surgery in all cases. The choice of surgical technique was based on MRI features (i.e., number of compression levels, sagittal alignment, stenosis characteristics, clinical presentation, and comorbidities). Anterior cervical discectomy and fusion was performed in 43% of the cases, and posterior laminectomy with fusion was performed in 57% (Table 1).

We have not identified intraoperative (i.e., nerve injury or hemorrhage) or postoperative (i.e., hematoma, infections, dysphagia, or axial/scapular pain) complications. Neurological deterioration was not found in any patient after surgery.

Statistical Analysis

Data analysis was performed using SPSS (version 23.0, IBM Corp.). Means and standard deviations were computed for demographic data (age and sex), preoperative metabolites (NAA, myo-inositol, choline, and glutamate-glutamine), and pre- and postoperative clinical scores (mJOA score, 9-HPT score, and walking time). Data were

then submitted to a 4 (metabolites) $\times$ 2 (groups: CSM vs control) $\times$ 2 (regions of interest: averaged left and right M1, cerebellum) analysis of variance (mixed ANOVA). Significant effects were further evaluated with Bonferroni-corrected t-tests. Due to the exploratory nature of this study, we did not perform corrections for multiple comparisons. In the CSM group, we also carried out paired t-tests to compare pre- versus postoperative clinical scores; Spearman correlation analysis to investigate the relationships between preoperative metabolites and pre- and postoperative clinical scores; and simple and multiple regression analysis for significant predictors (metabolites) from Spearman analysis. A p value < 0.05 was considered significant for all statistical tests.

Results

Preoperative Neurological Status

All patients had preoperative functional deficits as indicated by an mJOA score lower than 18 (Table 1), 20 suffered from difficulties using their upper extremities (mean mJOA-UE score 5.6 ± 0.9 ; 16 patients demonstrated greater impairment of the right upper extremity), 8 exhibited altered finger dexterity (9-HPT time 29.5 ± 47.2 seconds), and 16 reported gait difficulty (mean mJOA-LE score 5.6 ± 1.2 ; walking test 39.9 ± 23.5 seconds, with an average speed of 0.75 m/second).

Preoperative Metabolite Levels and Their Relationships With Preoperative Neurological Status

The mean metabolite levels in M1 and the cerebellum in each group are shown in Table 2 (with standard deviations and 95% confidence intervals).

Relative to controls, patients had significantly higher levels of choline across both M1s. This suggests an increase in cell membrane turnover and breakdown in these areas. However, we did not detect any significant between-group difference with respect to NAA, although there was a trend toward lower levels in patients in the left or right M1 (relative to levels in controls). Likewise, no statistically significant difference was detected between the CSM group and controls with respect to myo-inositol or glutamate-glutamine levels. Notably, significant correlations were found between choline and myo-inositol levels across M1 and the time to complete the 9-HPT ($r = 0.46$, $p = 0.04$, and $r = -0.52$, $p = 0.02$, respectively; Fig. 2A left panel). Including these 2 metabolites in a regression model, we found that choline and myo-inositol together explained 30% of the variance in preoperative dexterity ($p = 0.02$).

Although we failed to find significant differences in metabolite levels in the cerebellum in CSM patients compared with controls (Table 2), the levels of myo-inositol and glutamate-glutamine were positively correlated to mJOA-total scores ($r = 0.46$, $p = 0.04$, and $r = 0.56$, $p = 0.01$; Fig. 2A right panel), contributing 22% to preoperative neurological impairment (mJOA-total, $p = 0.06$). Glutamate-glutamine levels were also correlated with mJOA-LE scores ($r = 0.55$, $p = 0.02$), predicting 30% of variation in preoperative gait deficits ($p = 0.01$).

TABLE 2. Between-groups comparisons of mean metabolite levels (ratios relative to creatine) in M1 and the cerebellum

Variable	NAA/Cr	mIn/Cr	Cho/Cr	Glx/Cr
Left M1				
Control	1.60 ± 0.14 (1.53–1.67)	0.77 ± 0.09 (0.73–0.82)	0.23 ± 0.02 (0.22–0.24)	1.99 ± 0.31 (1.82–2.15)
CSM	1.54 ± 0.15 (1.48–1.62)	0.77 ± 0.12 (0.71–0.83)	0.25 ± 0.22 (0.24–0.26)	1.80 ± 0.39 (1.62–1.98)
	$F_{1,36} = 1.2, p = 0.3$	$F_{1,36} = 0.02, p = 0.9$	$F_{1,36} = 7.4, p = 0.01$	$F_{1,36} = 2.4, p = 0.1$
Right M1				
Control	1.62 ± 0.14 (1.53–1.70)	0.76 ± 0.08 (0.72–0.80)	0.21 ± 0.03 (0.19–0.22)	2.08 ± 0.44 (1.84–2.32)
CSM	1.60 ± 0.21 (1.49–1.70)	0.77 ± 0.12 (0.71–0.84)	0.24 ± 0.03 (0.22–0.26)	2.14 ± 0.47 (1.91–2.38)
	$F_{1,36} = 0.1, p = 0.8$	$F_{1,36} = 0.1, p = 0.7$	$F_{1,36} = 9.1, p = 0.005$	$F_{1,36} = 0.1, p = 0.7$
Left & right M1				
Control	1.61 ± 0.13 (1.49–1.54)	0.77 ± 0.06 (0.73–0.80)	0.22 ± 0.02 (0.21–0.23)	2.04 ± 0.28 (1.9–2.2)
CSM	1.56 ± 0.15 (1.55–1.68)	0.77 ± 0.12 (0.72–0.83)	0.25 ± 0.02 (0.24–0.26)	1.97 ± 0.33 (1.8–2.1)
	$F_{1,36} = 1.3, p = 0.3$	$F_{1,36} = 0.03, p = 0.9$	$F_{1,36} = 15.3, p < 0.001$	$F_{1,36} = 0.5, p = 0.5$
Cerebellum				
Control	0.87 ± 0.07 (0.80–0.98)	0.68 ± 0.09 (0.63–0.72)	0.27 ± 0.04 (0.25–0.29)	1.54 ± 0.41 (1.30–1.78)
CSM	0.89 ± 0.16 (0.84–0.91)	0.62 ± 0.09 (0.58–0.67)	0.25 ± 0.03 (0.23–0.26)	1.42 ± 0.41 (1.21–1.62)
	$F_{1,36} = 0.2, p = 0.7$	$F_{1,36} = 3.2, p = 0.1$	$F_{1,36} = 2.0, p = 0.2$	$F_{1,36} = 0.7, p = 0.4$

Cho = choline; Cr = creatine; Glx = glutamate-glutamine; mIn = myo-inositol.

Values are mean ± SD (95% CI) unless otherwise indicated; p values are for differences between the CSM and control groups.

Postoperative Assessment

Postoperative Neurological Status

Clinical assessment at 6 months after surgery showed a significant increase in mJOA scores, with the mean mJOA-total increasing from a preoperative value of 13.6 ± 2.0 to a postoperative value of 15.7 ± 1.7 ($p < 0.001$), indicating improvement in upper-extremity, lower-extremity, and sphincter function. Specifically for upper- and lower-extremity function, the mJOA-UE increased from 5.6 ± 0.9 to 6.6 ± 0.9 ($p < 0.001$) while the mJOA-LE increased from 5.6 ± 1.2 to 6.3 ± 1.0 ($p < 0.001$) (Fig. 2B left panel). Thirteen (62%) of 21 patients achieved an mJOA score ≥ 16 , which translates to minimal neurological impairment and social independence. Patients also showed a significant decrease in the time it took them to walk a 30-m distance (from 39.3 ± 23.5 seconds to 31.9 ± 11.1 seconds, $p = 0.02$; Fig. 2B right panel). We also found a trend toward a decrease in the average time to execute 9-HPT after surgery (from 29.5 ± 47.2 seconds to 19.6 ± 7.8 seconds, $p = 0.3$; Fig. 2B right panel).

Relationship Between Preoperative Metabolite Levels and Postoperative Neurological Status

The relationships between postoperative clinical scores and preoperative M1 and cerebellar metabolite levels, preoperative clinical scores, and patient age are presented in Tables 3 and 4.

Across left and right M1s, higher levels of myo-inositol and lower levels of choline correlated with shorter postoperative 9-HPT execution time ($p = 0.04$ and $p = 0.006$, respectively; Table 3). The regression models indicated that these 2 metabolites across M1s explain 8% of the variance in postoperative dexterity (Table 4). In the left M1, levels of NAA and glutamate-glutamine correlated positively with mJOA-UE scores ($p = 0.03$ and $p = 0.02$, respec-

tively) and explained 15% of the variance in postoperative upper-extremity sensorimotor disability (Table 4).

Significant correlations between levels of myo-inositol and glutamate-glutamine in the cerebellum and mJOA-LE scores were also found ($p = 0.04$ and $p = 0.005$, respectively), explaining 18% of the variance in postoperative gait measures (Table 4). The other cerebellar metabolites did not have a significant predictive value for surgical outcome.

Relationship Between Preoperative Clinical Scores and Postoperative Neurological Status

As expected,⁶⁸ preoperative 9-HTP, mJOA-UE, and mJOA-total scores were the main determinants of postoperative dexterity, upper-extremity disability, and neurological status (p varies between 0.01 and < 0.001 ; Table 3) and preoperative mJOA-LE and mJOA-total scores and time to walk 30 m predicted upper- and lower-extremity disabilities (p varies from 0.003 to < 0.001). Preoperative scores on the 9-HTP, mJOA-UE, and mJOA-LE explained 64%, 57%, and 70% of the variance in postoperative dexterity (9-HTP), upper-extremity sensorimotor (mJOA-UE), and lower-extremity motor (mJOA-LE) function, respectively (Table 4).

Relationship Between Age and Postoperative Neurological Status

Contrary to our expectations,⁶⁸ we failed to find a significant correlation between patient age and postoperative clinical status ($p > 0.05$, Table 3).

Relationships Between Combined Preoperative Metabolite Levels and Preoperative Clinical Scores and Postoperative Neurological Status

We studied whether an approach reflective of remote

A. Preoperative correlations between metabolites and myelopathy clinical severity

B. Clinical scores prior to and at six months after surgery

FIG. 2. A: Scatter plots showing the correlations between M1 levels of myo-inositol (mIn, gray circles) and choline (Cho, white circles) and preoperative 9-HPT scores (left panel), and between cerebellar levels of mIn and glutamate-glutamine (Glx, black triangles) and preoperative mJOA-total scores (right panel). Note that 1 patient was excluded from the right scatter plot due to an extremely long time to execute the clinical testing (234.5 seconds). **B:** Mean (+SD) preoperative (Pre) and postoperative (Post) clinical scores (left panel: mJOA-total [gray columns], mJOA-UE [mJOA-upper, gray-patterned columns], and mJOA-LE [mJOA-lower, white columns]; right panel: walking test [black columns] and 9-HPT [black-patterned columns]). * $p = 0.02$; ** $p < 0.001$. s = seconds.

cerebral damage and/or plasticity and preoperative neurological impairment could increase prediction accuracy. The contribution of M1 or cerebellar metabolites to postoperative clinical status was greatly strengthened by adding preoperative clinical metrics (for left and right M1, from 8% to 59%; for left M1, 5% to 73%; for right M1, 2% to 68%; for the cerebellum, 18% to 75%; Table 4). Notably, most of these combinations predicted postoperative clinical status more accurately than did preoperative clinical scores alone (left or right M1, 73% or 68% vs 64% preoperative clinical status alone; cerebellum, 75% vs 70%; Table 4).

Discussion

We explored, for the first time, whether ^1H -MRS measures of the damage and/or plasticity of the spared motor system induced by progressive CSM may be informative

as to the likelihood of achieving clinical gains after spinal decompression surgery. Three main results were revealed. First, the metabolic profile of M1 was altered prior to surgery in patients with CSM compared with controls, and certain metabolites were associated with upper-extremity sensorimotor deficits. As detailed below, these findings possibly reflect remote neuroinflammation triggered by progressive axonal deterioration during chronic spinal cord compression. The metabolic profile of the cerebellum was not altered, presumably reflecting insufficient compromise of the spinocerebellar and/or rubro- or reticulospinal tracts. However, certain cerebellar metabolites were associated with neurological dysfunction. Second, levels of certain metabolites in M1 and the cerebellum were associated with postoperative clinical status. This indicates that remote ^1H -MRS measures may provide insights into brain events that can be informative, at least partially, with

TABLE 3. Relationship between preoperative demographic data, clinical metrics, and ¹H-MRS metrics and postoperative clinical metrics

Preoperative Variable	Postoperative Metrics									
	9-HPT		mJOA-UE		mJOA-LE		mJOA-Total		Walking Test*	
	r	p Value	r	p Value	r	p Value	r	p Value	r	p Value
Demographic data										
Patient age	0.11	0.6	-0.12	0.6	0.10	0.7	0.19	0.4	-0.17	0.5
Preop clinical metrics										
9-HPT	0.97	<0.001	-0.59	0.005	-0.14	0.5	-0.50	0.02	0.08	0.7
mJOA-UE	0.76	<0.001	0.74	<0.001	0.44	0.05	0.69	<0.001	-0.29	0.2
mJOA-LE	-0.31	0.1	0.62	0.003	0.85	<0.001	0.78	<0.001	-0.63	0.003
mJOA-total	-0.54	0.01	0.74	<0.001	0.79	<0.001	0.87	<0.001	-0.52	0.02
WT-time	0.30	0.2	-0.21	0.4	-0.36	0.1	-0.32	0.2	0.93	<0.001
¹ H-MRS metrics										
Left & right M1										
NAA/Cr	-0.11	0.6	0.14	0.5	-0.35	0.1	-0.15	0.5	0.13	0.6
mIn/Cr	-0.46	0.04	0.31	0.2	0.04	0.9	0.21	0.4	-0.11	0.6
Cho/Cr	0.59	0.006	-0.28	0.2	0.05	0.8	-0.10	0.7	0.04	0.9
Glx/Cr	-0.34	0.1	0.28	0.2	-0.19	0.4	-0.05	0.8	0.10	0.7
Left M1										
NAA/Cr	-0.05	0.8	0.47	0.03	-0.08	0.9	0.27	0.2	0.12	0.6
mIn/Cr	-0.35	0.1	0.13	0.6	0.17	0.5	0.14	0.6	0.04	0.9
Cho/Cr	0.54	0.01	-0.24	0.3	-0.9	0.7	-0.17	0.5	0.19	0.4
Glx/Cr	-0.31	0.2	0.50	0.02	-0.08	0.7	0.32	0.2	0.15	0.5
Right M1										
NAA/Cr	-0.13	0.6	0.18	0.4	0.04	0.9	0.14	0.6	0.17	0.5
mIn/Cr	-0.41	0.08	0.26	0.3	0.24	0.3	0.22	0.3	-0.14	0.6
Cho/Cr	0.42	0.07	0.05	0.8	-0.22	0.4	-0.15	0.5	-0.06	0.8
Glx/Cr	0.04	0.9	0.09	0.7	0.09	0.7	0.18	0.5	-0.01	0.9
Cerebellum										
NAA/Cr	0.13	0.5	-0.15	0.5	0.06	0.8	-0.14	0.6	0.07	0.8
mIn/Cr	-0.32	0.2	0.39	0.1	0.46	0.04	0.39	0.1	-0.09	0.7
Cho/Cr	-0.34	0.2	0.32	0.2	0.37	0.1	0.31	0.2	-0.32	0.2
Glx/Cr	-0.18	0.5	0.20	0.4	0.63	0.005	0.46	0.06	-0.43	0.08

WT = walking test.

Boldface type indicates statistical significance.

* Results based on time needed to walk 30 m.

respect to achieving functional gains. Third, M1 or cerebellar metabolites combined with preoperative clinical metrics predict outcome better than the individual predictors alone. This suggests that ¹H-MRS measures might provide insights into biological mechanisms underlying recovery that could complement clinical assessments.

Alteration of M1 Metabolic Profile in CSM Patients

Consistent with our predictions, we found an altered metabolic profile across M1 in patients with CSM relative to analogous territory in age- and sex-matched controls. Specifically, we identified a significantly higher level of choline across these areas (see Table 2). Considering that the choline signal represents membrane phospholipid derivatives (see Freeman and Jenden²⁴ review), higher levels of choline signal are thought to reflect membrane degrada-

tion, demyelination, or glial proliferation.^{6,41} Indeed, a slow neuroinflammatory response was recently reported at the spinal cord level in humans^{3,73} and in an animal model.²¹ This process is likely to lead to chronic demyelination² and/or cause activation of microglia and release of additional toxic stimuli from other cells (e.g., astrocytes and neurons).⁵⁶ However, it is not known whether such neuroinflammatory events also exist in the remote M1 in this chronic condition. Our findings are the first evidence of possible neuroinflammation across M1 in patients suffering from CSM, and, considering the relationships between choline levels and neurological impairment and recovery (see below), these events are likely to be detrimental. It is important to note that the differences that we detected between CSM patients and controls were selective to choline and not evident in NAA, myo-inositol, or glutamate-glu-

TABLE 4. Results of regression analysis: relationship of ¹H-MRS metabolites (with and without preoperative clinical metrics) to postoperative clinical metrics

Variable	Adjusted R ² (%)	p Value
Outcome 1: 9-HPT		
Preop 9-HPT	64	<0.001
Left & right M1 (mIn + Cho)	8	0.2
Left M1 (mIn + Cho)	5	0.3
Right M1 (mIn + Cho)	2	0.4
Left & right M1 + preop 9-HPT	59	0.001
Left M1 + preop 9-HPT	73	<0.001
Right M1 + preop 9-HPT	68	<0.001
Outcome 2: mJOA-UE		
Preop mJOA-UE	57	0.000
Left M1 (NAA + Glx)	15	0.09
Left M1 + preop mJOA-UE	60	<0.001
Outcome 3: mJOA-LE		
Preop mJOA-LE	70	<0.001
Cerebellum (mIn + Glx)	18	0.09
Cerebellum + preop mJOA-LE	75	<0.001

tamine (Table 2). The lack of significant changes in NAA levels does not corroborate the findings of Kowalczyk et al.³⁸ On the one hand, this may reflect methodological differences: the use of larger spectroscopic voxel size (8 cm³ in their study vs 3.4 cm³ in our case), NAA measured only in the hand territory contralateral to the most affected hand (compared with averaged M1 or each M1; see Table 2), or higher field strength than ours (3 T vs 1.5 T). On the other hand, the failure to find significant differences in NAA levels is consistent with the above-mentioned report on an animal model of SCI.²¹ Further, higher NAA levels were reported in motor cortex at 0.5–2 years after incomplete SCI in humans.⁵⁵ In the face of these contradictory findings, it is clear that we are missing key facts about dynamic temporal changes of NAA (and other metabolites) at the cortical level in CSM. Clearly, more work is needed.

By contrast, our myo-inositol and glutamate-glutamine findings were similar to those reported by Kowalczyk and colleagues.³⁸ However, the failure to find significant changes in myo-inositol is an unexpected result because neuroinflammation, reported here, is likely to be driven by active microglia.¹⁷ Nonetheless, myo-inositol is involved in other cellular processes,²³ and the changes in myo-inositol and choline cannot necessarily be interpreted as reflecting a single mechanism.⁷⁴

To provide a functional context for the metabolite measures, we also collected data on clinical impairment at the same time point as MRS. We found that lower levels of choline and higher levels of myo-inositol across M1 were associated with shorter time to execute the 9-HPT. Put differently, less neuroinflammation and higher glial recruitment (possibly involved in long-term synaptic plasticity^{30,33,36,58,70}) across M1 relate to better dexterity. Notably, when taken together, these M1 metrics explain about 30% of variance in preoperative dexterity.

Inconsistent with our prediction, we found unaltered

metabolic profile of the cerebellum. It is possible that the tract's compromise was insufficient to mediate significant metabolic change at this level or that the cerebellum appears to be less affected by chronic spinal cord compression. Of note, similar findings using ¹H-MRS of the thalamus and striatum have been reported after SCI,²¹ suggesting that metabolic changes could be different at different levels of the neuraxis. We, however, found significant positive correlations between the levels of myo-inositol and glutamate-glutamine in the cerebellum and the mJOA-total scores, contributing in a proportion of 22% to the variance of neurological impairment. Likewise, the levels of glutamate-glutamine explain about 30% of variance of lower-extremity motor disabilities. Thus, increased glial involvement and excitability in the cerebellum are likely to be associated with preoperative higher function of both upper and lower extremities.

Taken together, these findings suggest that, although we are still far from identifying the specific molecular forces driving metabolic changes, this approach generates metrics that quantify the amount of injury and/or plasticity upstream from the SCI that seems to correlate with neurological/functional impairment.

Predictors of Postoperative Neurological Status

M1 and Cerebellar Metabolic Profiles

All patients achieved significant functional improvement after surgery (Fig. 2B), and postoperative clinical status was significantly associated with the preoperative levels of certain metabolites across M1 and the cerebellum (see Tables 3 and 4). Specifically, when assessing the contribution of individual metabolites to surgery outcome, higher levels of dexterity were associated with lower levels of choline and higher levels of myo-inositol across left and right M1s, while higher levels of upper-extremity sensorimotor function were associated with higher NAA and glutamate-glutamine levels in the left M1. The latter is not a surprising finding because most of our patients suffered from difficulties using their right upper extremity. Taken together, these findings suggest that patients with less neuroinflammation and neuronal metabolic depression in M1 have the potential to reorganize (as indexed by higher glial recruitment and increased excitability) in parallel with clinical gains. Although the contribution of these events to surgical outcome is low (for left M1, 5% or 15% depending on the outcome measure), these findings corroborate the findings of prior functional MRI studies suggesting a major role of both M1s in the recovery of dexterous function in patients with CSM^{16,18,31,66} or SCI.^{43,47} While those studies employed metrics of M1 activation, we explored the contribution to motor gain made by metabolites related to a specific cell or system within this area. Therefore, the functional recovery of upper-extremity sensorimotor function in these patients may reflect, in part, the potential of M1 to reorganize at the cellular level.

We also found meaningful correlations between preoperative levels of myo-inositol and glutamate-glutamine in the cerebellum and the postoperative extent of lower-extremity disability (Table 3). One interpretation is that patients with a high degree of involvement of glial cells and increased excitability were able to improve their mo-

tor function, possibly indicating the presence of an available biological substrate (with a contribution of 18%; Table 4) needed to achieve those gains.

The relationships presented here do not necessarily imply causation, but we hope that these data will act as a starting point for further research to test this hypothesis in larger samples.

Preoperative Clinical Metrics

In line with recent studies,^{67–69} our findings showed that preoperative clinical scores had high sensitivity in predicting neurological outcome after surgery in these patients (Table 4).

Combination of M1 and Cerebellar Metabolic Profiles and Preoperative Clinical Metrics

Because multimodality approaches may provide rich insights in this context,^{20,45,49} we also explored the combination of ¹H-MRS measures and preoperative clinical metrics in predicting the surgery outcome. We found that the predictive values of spectroscopic metrics were significantly improved by adding the preoperative clinical metrics into the model (see Table 4). One interpretation of this finding is that CSM patients, in whom the neurological improvement following surgery is absent or partial, might have cerebral and/or cerebellar alterations that are incompatible with recovery. Our models also showed an improved predictive value of the preoperative clinical metrics. This finding precisely echoes the results of prior studies in brain damage^{5,14} and spinal cord,^{43,47} suggesting that functional recovery could be largely determined by both the damage per se and remote brain damage and/or reorganization. Therefore, our current results indicated that behavioral recovery in patients with CSM might reflect both the direct effect of decompression surgery and the cerebral/cerebellar potential to reorganize at the cellular level.

Study Limitations

There are several limitations to this study. First, we quantified the levels of metabolites as ratios relative to levels of creatine, assuming that this signal is relatively constant in the normal healthy brain.⁶² Although this approach eliminates the need to account for changes in partial tissue volume between participants, the use of ratios may introduce more variability.³⁹ Nevertheless, the findings of this study provide evidence for a significant increase in choline levels across M1 relative to controls. Second, only symptomatic patients have been included, limiting the generalizability of the current findings to asymptomatic patients. Third, all our patients were prescribed pain medication on an “as-needed” basis. However, analgesic drugs are likely to induce changes in glutamate levels without affecting other metabolites.²⁹ Our findings of significant choline changes and no glutamate-glutamine changes help to rule out this factor. Fourth, the specific duration of the symptoms was not recorded, and therefore we were unable to investigate the relationship between this variable and the metabolic profiles. Fifth, the heterogeneity among the patients with regard to CSM etiology limits the interpretation of our data. Finally, we and others have described metabol-

ic changes in intact spinal cords in these patients^{1,20,32,60} (C. S. Craciunas et al: Proton MRS measurements in cervical spinal cord predict functional recovery after decompressive surgery in cervical spondylotic myelopathy, presented at EuroSpine 2013, Liverpool, UK), and this reorganization may contribute to the recovery. Future studies are required to determine the relative contributions of different sites of plasticity and the conditions in which they apply differentially.

Conclusions

In summary, using a relatively homogeneous cohort, we demonstrated the potential of ¹H-MRS metrics to provide insights into cerebral and cerebellar metabolic profiles in patients suffering from CSM. We also found that certain cerebral and cerebellar metabolites may be informative for neurological impairment and recovery. Such insights would help physicians to 1) predict which patients would benefit the most from surgery; 2) set realistic postoperative therapeutic goals, by selection of individualized rehabilitation strategies based on likely recovery potential; and 3) manage patients' expectations from surgery. Likewise, they can help the physician make a decision, especially in cases involving high surgical risk. Finally, such insights can also be helpful as an individual prognostic indication for patients and relatives. We also advocate the power of the multivariate technique in developing prediction models in patients suffering from this increasingly important clinical entity.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: Cirstea, Craciunas. Acquisition of data: Craciunas, Gorgan. Analysis and interpretation of data: Cirstea, Craciunas, Lee, Burris. Drafting the article: Cirstea, Ianosi. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Cirstea. Statistical analysis: Cirstea, Ianosi. Administrative/technical/material support: Craciunas, Gorgan, Lee. Study supervision: Cirstea, Craciunas.

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