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ORIGINAL ARTICLE

High-resolution nuclear magnetic resonance spectroscopic study of metabolites in the cerebrospinal fluid of patients with cervical myelopathy and lumbar radiculopathy

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Abstract There have been few reports describing substances related to oxidative and intermediary metabolism in the cerebrospinal fluid (CSF) in patients with spinal degenerative disorders. This study investigated whether the concentrations of metabolites in the CSF differed between patients with spinal degenerative disorders and controls, and whether the concentrations of these metabolites correlated with the severity of symptoms. CSF samples were obtained from 30 patients with cervical myelopathy (Group M), 30 patients with lumbar radiculopathy (Group R), and 10 volunteers (control). Metabolites in these CSF samples were measured by nuclear magnetic resonance spectroscopy. There were no differences in the concentrations of lactate, alanine, acetate, glutamate, pyruvate, or citrate between Groups M and R, between Group M and the control, or between Group R and the control. In Group M, neither symptom duration nor the Japanese Orthopaedic Association score correlated with the concentration of any metabolite. In Group R, the symptom duration positively correlated with the concentration of lactate, glutamate, and citrate in CSF. The duration of nerve root block showed a negative correlation with the concentrations of acetate in CSF of the patients in Group R. In patients with lumbar radiculopathy, there is a possibility of increased aerobic metabolic activity or decreased gluconeogenic activity in patients with shorter symptom duration, and increased aerobic metabolic activity in patients with severe inflammation around a nerve root.

Keywords Cerebrospinal fluid · Cervical myelopathy · Lumbar radiculopathy · Metabolites · Nuclear magnetic resonance spectroscopy

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Introduction

Cervical myelopathy results from compression of the spinal cord in patients with cervical spondylosis, ossification of the posterior longitudinal ligament, or disc herniation. Lumbar radiculopathy occurs as a result of compression of the nerve root by herniated disc material, osteophytes, and/or ligamentum flavum. Under these conditions, neural tissue damage can occur, and several authors have reported that specific cytokines increase in the cerebrospinal fluid (CSF) of patients with spinal degenerative disorders such as cervical spondylotic myelopathy and lumbar disc herniation [5, 7, 18]. These cytokines were reported to be produced from the nerve and glial cells and released into the CSF [13, 17, 24, 25]. Moreover, the cytokine concentration in the CSF is elevated by increased permeability of the blood–nerve barrier caused by spinal degenerative disorders [2, 27, 28]. However, there have

been only a few reports of metabolites such as lactate and pyruvate in the CSF of patients with spinal degenerative diseases [6, 12, 16, 33].

High-resolution nuclear magnetic resonance (NMR) spectroscopy is useful for the measurement of key substances on oxidative and intermediary metabolism [12, 19, 30]. This technique has been applied to studies of metabolites in CSF of patients with various diseases such as multiple sclerosis (MS) [12, 15], tumors [12, 22], infection [12], and amyotrophic lateral sclerosis [10, 11, 20, 21, 23, 26]. Regarding spinal degenerative diseases, a few authors only reported metabolites in CSF compared with the control [6, 12, 33].

This study investigated whether the concentrations of metabolites in the CSF differed between patients with spinal degenerative disorders and controls. We further studied the relationships between the concentrations of these metabolites and the severity of symptoms; in patients with lumbar radiculopathy, we examined the relationships between metabolites and the duration of nerve root block.

Materials and methods

CSF samples were obtained from 30 patients with cervical myelopathy (Group M) and 30 patients with lumbar radiculopathy (Group R) by lumbar puncture prior to myelography, and 10 volunteers (control) who underwent lumbar spinal anesthesia for removal of devices after osteosynthesis. None of the volunteers in the control group had neck, back, or low back pain, or any neurological symptoms. We also confirmed that they did not show neurological deficits or positive tension sign. The average ages were 64.1 (range 46–82 years), 58.7 (range 25–85), and 62.9 years (range 26–88) in Groups M, R, and the control, respectively. There was no significant difference in age between Groups M and R, between Group M and the control, or between Group R and the control. There were 24 men and 6 women in Group M, 24 men and 6 women in Group R, and 7 men and 3 women in the control. In Group M, there were 22 patients with cervical spondylotic myelopathy (CSM), 7 with ossification of the posterior longitudinal ligament (OPLL), and 1 with cervical disc herniation (CDH). Group R consisted of 20 patients with lumbar disc herniation (LDH) and 10 with lumbar canal stenosis (LCS). In Group R, L4, L5, and S1 nerve roots were involved in 4, 21, and 5 patients, respectively.

The CSF samples were obtained by lumbar puncture and stored immediately at −80°C. At least 6 h before CSF sampling, all patients discontinued any medication. All specimens were clear and transparent without any precipitation or suspended materials. Therefore, the analysis was carried out without further treatment of the specimens. Deuterated water, 0.06 ml, was added to 0.54 ml CSF specimens at a concentration of 10% of the whole volume in a 5-mm NMR tube prior to measurement for the frequency lock of irradiation.

The free induction decays (FIDs) of the ^{1}H-NMR were recorded on a Varian Unity 500 spectrometer equipped with a 5-mm $^{1}H\{^{15}N\text{-}^{31}P\}$ pulsed field gradient indirect probe operating at 500 MHz for ^{1}H. Measurement was carried out at 27°C with a spectral width at 5.2 kHz. The FIDs of 256 transients were accumulated over 32k data points, using a 45° radio frequency pulse and a 10-s pulse delay. An exponential line broadening of 0.3 Hz was used. The predominant water resonance was suppressed by the presaturation method with a saturation power of 45.3 Hz during a delay time of 1.5 s. The chemical shifts of the signals referred to the internal standard of 1 mmol/l trimethyl-silyl-propionate-tetradeuterate (TSP-d_4). Quantitative analyses were carried out by integration of the area of the signals, and the concentrations were calculated from the areas of metabolites with respect to the area of the TSP-d_4 resonance after correction of the number of protons.

Two-dimensional correlation spectrum was measured for the assignment of the peaks by double quantum filtered correlation spectroscopy (DQF-COSY) with the presaturation method for water suppression. The spectral widths in the F1 and F2 axes were 5.2 kHz. Before the Fourier transformation, the Gaussian function was multiplied for apodization. The FIDs of 256 transients in the F1 direction and 32 transients in the F2 direction were accumulated in $2k \times 2k$ data points. ^{1}H-NMR spectroscopic data were obtained by one of the current authors (SM) who was blinded to the demographic data and other patient findings.

We evaluated differences in the concentrations of metabolites among the three groups, and the relationships between these metabolites and the severity of conditions or symptom durations were also evaluated. The mean symptom durations were 25.1 months (range 1–144 months) and 81.0 months (range 2–320 months) in Groups M and R, respectively. The severity of cervical myelopathy was evaluated using a scoring system for cervical myelopathy by the Japanese Orthopaedic Association [32] (JOA score-C). The highest possible JOA score-C is 17 points. The mean JOA score-C in Group M was 10.3 points (range 5.5–13.0). The severity of lumbar radiculopathy was evaluated using the assessment of treatment for low back pain by the Japanese Orthopaedic Association [8] (JOA score-L). The highest possible JOA score-L is 29 points. The mean JOA score-L in Group R was 11.9 points (range 3–22). To evaluate the relationships between neurological deficits in Group R and the concentrations of the metabolites in CSF, the sum of motor disturbance and sensory disturbance on JOA score-L (neurological deficits score) was calculated. The highest possible score is 4 points. The mean

Table 1 Concentrations of metabolites in cerebrospinal fluid specimens from the three groups

Group	Lactate (μmol/l)	Alanine (μmol/l)	Acetate (μmol/l)	Glutamate (μmol/l)	Pyruvate (μmol/l)	Citrate (μmol/l)
M	1,681.37 ± 758.62	72.05 ± 44.51	35.91 ± 26.08	527.08 ± 205.31	54.49 ± 35.82	306.16 ± 142.48
R	1,547.70 ± 721.09	65.80 ± 43.08	36.15 ± 23.83	463.39 ± 167.62	52.86 ± 41.21	250.74 ± 105.86
Control	1,629.56 ± 614.27	66.09 ± 36.97	31.54 ± 20.26	540.82 ± 160.29	62.06 ± 36.53	292.19 ± 182.37

Values are given as mean ± standard deviation

Table 2 Correlation coefficients (a probability value) between concentrations of metabolites and parameters of patients with cervical myelopathy

	Lactate	Alanine	Acetate	Glutamate	Pyruvate	Citrate
Sympton duration	−0.340 (0.066)	−0.171 (0.366)	−0.200 (0.288)	−0.167 (0.378)	−0.146 (0.442)	−0.265 (0.158)
JOA score-C	0.129 (0.498)	0.314 (0.091)	0.100 (0.601)	0.320 (0.084)	0.117 (0.538)	0.157 (0.407)

JOA score-C a scoring system for cervical myelopathy by the Japanese Orthopaedic Association

Table 3 Correlation coefficients (a probability value) between concentrations of metabolites and parameters of patients with lumbar radiculopathy

	Lactate	Alanine	Acetate	Glutamate	Pyruvate	Citrate
Sympton duration	0.483 (0.007)**	0.359 (0.052)	0.150 (0.429)	0.394 (0.035)*	0.284 (0.135)	0.381 (0.038)*
JOA score-L	−0.194 (0.303)	−0.191 (0.312)	−0.352 (0.056)	−0.296 (0.119)	−0.072 (0.710)	−0.128 (0.501)
NDS	−0.115 (0.544)	−0.255 (0.173)	−0.187 (0.323)	−0.250 (0.191)	0.005 (0.978)	−0.179 (0.343)
DNRB	0.080 (0.691)	0.156 (0.437)	−0.444 (0.020)*	−0.024 (0.906)	0.154 (0.451)	0.212 (0.289)

JOA score-L the assessment of treatment for low back pain by the Japanese Orthopaedic Association, *NDS* neurological deficit score, *DNRB* duration of nerve root block

* $p < 0.05$, ** $p < 0.01$

neurological deficits score in Group R was 2.2 points (range 0–4). In addition, the relationships between the metabolites and duration of nerve root block were evaluated in Group R. Just after CSF collection, a 22-gauge spinal needle was inserted into the involved nerve root sleeve with an image intensifier and 1 ml of 1.0% lidocaine HCl (Xylocaine®, Astra Zeneca, London, United Kingdom) and 2 mg of betamethasone (Rinderon®, Shionogi Co. & Ltd., Osaka, Japan) were injected after radiculography to ensure appropriate insertion. The interval until a patient first required an analgetic after selective nerve root block was defined as the duration of nerve root block.

Mann–Whitney *U* test was used for intergroup comparison. Correlation was evaluated with Spearman's rank sum test. A probability value less than 0.05 was considered significant. All statistical analyses were performed on SPSS.

Results

Lactate, alanine, acetate, glutamate, pyruvate, and citrate were detected in CSF from all patients. There were no significant differences in the concentrations of any metabolite between Groups M and R, between Group M and the control, or between Group R and the control (Table 1).

In Group M, symptom duration or JOA-C did not correlate with the concentration of all metabolites (Table 2).

In Group R, symptom duration positively correlated with the concentration of lactate ($p = 0.007$), glutamate ($p = 0.035$), and citrate ($p = 0.038$); however, there was no correlation with the concentrations of alanine, acetate, or pyruvate. JOA score-L or neurological deficits score did not correlate with the concentration of all metabolites. The duration of nerve root block showed a negative correlation with the concentration of acetate ($p = 0.020$); however, there was no correlation with the concentrations of lactate, alanine, glutamate, pyruvate, or citrate (Table 3). There was no difference in the concentration of any metabolite between patients with disc herniation and those with spinal canal stenosis.

Discussion

Our study has some limitations. Firstly, the CSF samples were obtained only from patients undergoing myelography. Myelography was performed for patients who were

candidates for surgery. Therefore, the patients in this study had moderate to severe symptoms, and so the current study may contain bias. Secondly, we did not perform magnetic resonance imaging studies for the volunteers in the control group to confirm that they did not have asymptomatic disc herniation or disc degeneration. Several previous reports [4, 9, 29, 31] demonstrated many asymptomatic subjects with an abnormal disc or facet joint on MRI, and Boden et al. [4] reported that only 1 of 14 asymptomatic subjects aged 60–80 years old showed normal discs. To avoid an age difference among the three groups, volunteers aged over 60 years old were required; however, it is extremely difficult to collect volunteers in this age group without any abnormal findings on spinal MRI. We confirmed that the volunteers did not have neck, back or lower back pain, or any neurological symptoms. Moreover, the volunteers were negative for neurological and tension signs. Those clinical findings suggested the absence of chemical or mechanical reactions in the spine in these volunteers. Thirdly, to avoid an age difference among the three groups, we included patients with CSM, OPLL, and CDH in Group M, and those with LDH and LCS in Group R. The patients with lumbar radiculopathy caused by LDH were younger than those with CSM; therefore, the age differences could be significant if this study had only included patients with CSM and LDH. We showed that there were no differences in the concentration of any metabolite between patients with LDH and those with LCS; however, there is a possibility that the data in this study were affected by a variety of disease conditions. Fourthly, symptom durations in our series ranged from 1 month to over 10 years. In some patients with longer duration of disease, it was difficult to confirm the precise onset of disease. Based on their medical records, the time when they first experienced numbness in their extremities was regarded as the onset of disease. However, there is a possibility that their numbness did not arise from any spinal disorder; if not, our results could have been affected.

To our knowledge, there have been few previous reports [6, 12, 16, 33] of ^{1}H NMR studies of CSF on patients with degenerative spinal disorders. However, these previous studies simply compared the metabolites in the CSF of patients with those of control samples. This is the first report of correlations between the concentration of metabolites in CSF from patients with spinal degenerative disorders and the severity of disease as indicated by JOA score and the duration of nerve root block. Koschorek et al. [12] previously studied high-resolution ^{1}H NMR spectroscopy of CSF from 29 patients with LDH and found that the relative concentration of acetate in CSF of patients with LDH differed from those of the control group. Zwart et al. [33] reported that the concentrations of lactate, pyruvate, and alanine in CSF from patients with disc protrusion or herniation were significantly lower than those of the control group. In another study by Zwart et al. [6], the concentrations of glucose, lactate, alanine, creatinine, and inositol in CSF from patients with LDH were significantly lower than those in age-matched controls. They also showed significant decreases in the concentrations of glucose and inositol in patients with LCS compared with those in age-matched controls. Regarding CSF from patients with cervical myelopathy, Meshitsuka et al. [16] demonstrated that endogenous ethanol was detected in 10 of 20 patients and concluded that the concentration of endogenous ethanol may be increased as the final product of enhanced glycolysis [14], or may be synthesized through an unknown pathway in some diseases as severe stimuli to the spinal cord.

Regarding other diseases, Koschorek et al. [12] also reported that in CSF from patients with tumors, MS, and infection, distinct differences in the concentrations of putrescine, citrate, valine, α-alanine, acetate, creatinine, glucose, β-hydroxy-butyric acid, glutamine, and creatine have been observed in comparison to those in the control group. Lynch et al. [15] reported that acetate levels were significantly higher in MS patients; otherwise, formate levels were significantly lower than the controls. They also showed that lactate and glutamine levels were not significantly different between CSF of MS and in that of the control, while another study [1] demonstrated that lactate and glutamine levels were significantly lower in MS patients than in control.

Pyruvate is intermediate in the catabolism of glucose and alanine [3]. Glucose is converted to pyruvate during aerobic glycolysis and lactate during anaerobic glycolysis. In the gluconeogenic pathway, lactate is retrogradely converted to pyruvate. Pyruvate is also formed in the degradation of amino acids such as alanine. Therefore, glucose, lactate, and alanine can be converted to pyruvate and then acetyl coenzyme A (CoA) for use in tricarboxylic acid (TCA) cycle. The initial step of the TCA cycle is catalyzed by citrate synthase. This highly exergonic reaction commits the acetyl group to citrate formation and complete oxidation in the TCA cycle. Glutamate can be converted to α-ketoglutarate in the gluconeogenic pathway for use in TCA cycle. In the current study, we found that symptom duration positively correlated with the concentration of lactate, glutamate, and citrate in CSF of patients with lumbar radiculopathy. Citrate and metabolites formed by lactate and glutamate can be used in the TCA cycle; therefore, there may be decreased aerobic metabolic activity or increased gluconeogenic activity in patients with longer symptom duration. We also demonstrated that the duration of nerve root block showed a negative correlation with the concentration of acetate in Group R. Acetate can be converted to acetyl CoA by acetate kinase for use in the

TCA cycle [3]. Selective nerve root block including steroids can have anti-inflammatory effects; therefore, a lower concentration of acetate in the CSF suggests the occurrence of more severe inflammation around the nerve root. There is a possibility of increased aerobic metabolic activity in patients with severe inflammation around a nerve root. However, we could not find any difference or any relationship in CSF samples of patients with cervical myelopathy. The discrepancies between our data and those of previous reports might be attributed to cross-sectional analysis of the metabolic process.

Conclusions

Unfortunately, we could not find any significant differences in the metabolites in CSF between patients with cervical myelopathy and the control, or between those with lumbar radiculopathy and the control. The symptom duration positively correlated with the concentration of lactate, glutamate, and citrate in CSF of patients with lumbar radiculopathy, suggesting decreased aerobic metabolic activity or increased gluconeogenic activity in the patients with longer symptom duration. We also demonstrated that the duration of nerve root block showed a negative correlation with the concentration of acetate in CSF in patients with lumbar radiculopathy. There may be increased aerobic metabolic activity in patients with severe inflammation around the nerve root.

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