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Correlation of cerebral spinal fluid pH and HCO_3^- with disease progression in ALS

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal disease, which is characterized by progressive degeneration of spinal and bulbar innervating motor neurons. However, the underlying mechanisms of motor neuron death remain poorly understood. Several candidate disease biomarkers have been detected in cerebrospinal fluid of ALS patients. The present study analyzed various cerebral spinal fluid gas parameters in ALS patients and compared these values to controls, as well as patients with cervical spondylosis, Parkinson syndrome, and spinocerebellar degeneration. Cerebral spinal fluid pH positively correlated with the ALS functional rating scale in total and limb-type ALS patients. In addition, cerebral spinal fluid pH positively correlated with shorter disease duration (less than 22 weeks). These results suggested that cerebral spinal fluid pH provides a biomarker for ALS and could reflect mechanisms of disease progression in ALS patients.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal disease characterized by progressive degeneration of spinal and bulbar innervating motor neurons [1]. Approximately 5–10% of patients have a genetically inherited form of the disease known as familial ALS (FALS). Our previous report and others have shown that approximately 20% of FALS patients have mutations in the superoxide dismutase 1 (SOD1) gene [2,3]. However, the mechanisms underlying slow progressive motor neuron death remain poorly understood.

Biological markers are objectively measured and evaluated as indicators of normal and pathogenic biological processes. The identification of biomarkers provides important advancements in medicine, which could lead to an improved understanding of disease pathogenesis and provide surrogate diagnostic and prognostic endpoints [4]. Several candidate biomarkers of disease progression have been investigated in ALS patients, such as raised concentrations of neurofilament protein, high concentrations of glial cell line-derived neurotrophic factor (GDNF), low levels of vascular endothelial growth factor (VEGF), and decreased levels of erythropoietin in cerebrospinal fluid (CSF) [5–10]. We have previously reported elevated MCP-1 and MCP-1/VEGF ratios in the CSF of ALS patients [11]. Results have suggested that CSF is an important source for biomarkers in ALS, since the CSF compartment is in close anatomical contact with the cerebral and spinal motor neurons involved in ALS, and biochemical changes should reflect changes in disease condition [12,13].

Gas analysis of CSF has been utilized for more than 30 years [14], and has been a useful prognostic or diagnostic marker for coma and head trauma [15–20]. However, these methods have not been utilized with ALS patients. Therefore, the present study analyzed various CSF gas parameters of ALS patients and compared these values to normal controls, as well as patients with cervical spondylosis (CS), Parkinson syndrome (PS), and spinocerebellar degeneration (SCD).

2. Material and methods

2.1. Patients

The present study comprised 12 controls (7 male and 5 female), 9 CS patients (7 male and 2 female), 14 PS patients (7 male and 7 female), 20 SCD patients (10 male and 10 female), and 38 ALS patients (23 male and 15 female). The PS group included Parkinson's disease (PD, n = 7), progressive supranuclear palsy (PSP, n = 3), and corticobasal degeneration (CBD, n = 4). The SCD group included multiple system atrophy (MSA, n = 10), cortical cerebellar atrophy (CCA, n = 3), spastic paraplegia (SP, n = 6), and dentatorubral-pallidoluysian atrophy (DRPLA, n = 1). Clinical and radiological diagnoses were made of CS, PS, and SCD.

ALS patients were diagnosed according to the El Escorial revised diagnostic criteria [21]. The present study was performed on 38 ALS

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS functional rating scale; CBD, corticobasal degeneration; CCA, cortical cerebellar atrophy; CS, cervical spondylosis; CSF, cerebrospinal fluid; DRPLA, dentatorubral-pallidoluysian atrophy; FALS, familial ALS; GDNF, glial cell line-derived neurotrophic factor; LDH, lactate dehydrogenase; MSA, multiple system atrophy; PBP, primary bulbar palsy; PD, Parkinson's disease; PS, Parkinson syndrome; PSP, progressive supranuclear palsy; SP, spastic paraplegia; VEGF, vascular endothelial growth factor.

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Table 1
Demographic data of the normal and the patients included in this study.

Cases	Normal Control	Cervical Spondylosis (CS)	Parkinson Syndrome (PS)	Spinocerebellar Degeneration (SCD)	Amyotrophic Lateral Sclerosis (ALS)
	n = 12	n = 9	n = 14	n = 20	n = 38
Gender (M / F)	7/5	7/2	7/7	10/10	23/15
Onset age (mean age ± S.D.)		58.1 ± 10.4	59.4 ± 17.4	53.7 ± 15.2	64.2 ± 10.4
Duration (mean month ± S.D.)		25.9 ± 23.5	30.6 ± 19.5	63.3 ± 61.6	22.4 ± 20.8
Examined age (mean age ± S.D.)	63.8 ± 18.8	59.1 ± 10.3	65.9 ± 8.8	58.2 ± 14.9	65.5 ± 10.6

patients (23 male and 15 female). No familial case was present; 28 patients presented with limb-type ALS, and the remaining 10 patients presented with primary bulbar palsy (PBP)-type ALS. Patients with respiratory failure or mechanical ventilation were not included. 31 of 38 ALS patients were taking riluzole.

Controls were suffered from non-organic neurological symptoms, such as headache or lower back pain. They had to undergo lumbar puncture for diagnostic reasons.

All enrolled patients and controls were admitted to Okayama University and Kurashiki Heisei Hospitals from September 2008 to February 2011.

2.2. Methods

All subjects (controls and patients) underwent lumbar puncture at L3/L4 or L4/L5. After the initial 10 ml CSF was eluted for cell counts, as well as protein, glucose, lactate, and pyruvate levels, a total of 0.5 ml CSF was collected into sterile 2.5-ml syringes. To avoid contact with air during and after collection, a small air space in the 2.5-ml syringe neck was replaced with physiological saline in advance. A total of 0.5 ml arterial blood was also obtained. Gas analyses for pH, pO_2, pCO_2, and HCO_3^- from CSF and arterial blood were performed using an ABL 800 (Radiometer, Copenhagen) blood gas analyzer.

2.3. Statistical analysis

For statistical analysis, one-way factorial ANOVA was used. Pearson product-moment correlation coefficient was used to analyze the association between clinical and CSF data. A value of $P<0.05$ was considered significant.

3. Results

3.1. Clinical characteristics

The onset ages of groups were as follows: CS 58.1 ± 10.4 (years, mean ± SD); PS 59.4 ± 17.4; SCD 53.7 ± 15.2; and ALS 64.2 ± 10.4. The durations of groups were as follows: CS 25.9 ± 23.5 (months, mean ± SD); PS 30.6 ± 19.5; SCD 63.3 ± 61.6; and ALS 22.4 ± 20.8. The examined ages of groups were as follows: control 63.8 ± 18.8 (years, mean ± SD); CS 59.1 ± 10.3; PS 65.9 ± 8.8; SCD 58.2 ± 14.9; and ALS 65.5 ± 10.6. There were no differences in onset age, durations, or examined ages between groups (Table 1). Also, there were no significant differences in onset age, duration of disease or examined age between controls and disease groups (data not shown).

3.2. CSF pH

The arterial blood pH of groups was as follows: control 7.41 ± 0.02 (mean ± SD); CS 7.41 ± 0.02; PS 7.41 ± 0.03; SCD 7.40 ± 0.03; and ALS 7.41 ± 0.02 and (Fig. 1, upper panel). The CSF pH of groups was as follows: control 7.33 ± 0.05 (mean ± SD); CS 7.33 ± 0.02; PS 7.33 ± 0.03; SCD 7.33 ± 0.04; and ALS 7.33 ± 0.02 (Fig. 1, lower panel). CSF pH values were generally less than arterial blood pH by an average of 0.08 in each group, although there were no significant differences between control and disease groups. Subtypes of ALS patients (limb-type *vs.* PBP-type) did not exhibit significant differences. However, different subgroups of ALS patients with disease severity exhibited lower CSF pH values in mild ALS patients (ALSFRS-R ≥ 40) ; 7.32 ± 0.02, compared with more severe ALS patients (ALSFRS-R < 40) ; 7.34 ± 0.02, total ALS patients, controls, and the remaining four disease groups, although the differences were not statistically significant (Fig. 1, right). In addition to the pH values, $P_{CSF}O_2/PaO_2$, $P_{CSF}CO_2/PaCO_2$, and CSF HCO_3^- values were not significantly different among the control group, the four disease groups, and the ALS subtypes groups, as well as in pO_2, pCO_2, and HCO_3^- values of CSF and arterial blood (data not shown).

Scatter plots for the relationships between age of onset (year), duration of disease (month), ALS functional rating scale (ALSFRS-R), and pH of arterial blood or CSF are shown for the ALS patients in Fig. 2. The limb-type patients are represented by filled diamonds and the PBP-type patients by open circles. As shown in the upper panels of Fig. 2, arterial blood pH did not correlate with age of onset, disease duration, or ALSFRS-R, and there was no significant difference between limb- or PBP-types in arterial blood pH. Although CSF pH did not correlate with age of onset or disease duration, it positively correlated with ALSFRS-R in the total ALS patient group [$r = -0.52$ (Fig. 2, right lower panel), solid line, $^{**}P<0.01$] and limb-type patients [$r = -0.53$ (Fig. 2, right lower panel), dotted line, $\#\#P<0.01$], but not in PBP type patients [$P>0.05$ (Fig. 2 right lower panel), open circles].

The present ALS patients with long disease durations (>23 months) exhibited mild symptoms (high ALSFRS-R scores) in limb- and PBP-

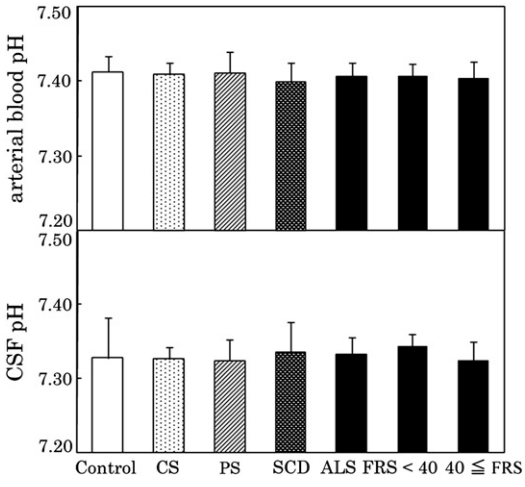

Fig. 1. (Left) The bar graphs show pH values of arterial blood (upper) and CSF (lower) in normal control subjects (control) and patients with CS, PS, SCD, and ALS. (Right) The two black bars show pH values of arterial blood and CSF of ALS subgroups divided into mild (FRS<40) and severe (40≤FRS) symptoms, respectively. FRS; ALS functional rating scale (ALSFRS-R).