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Effects of age and glucose levels on lactate levels in cerebrospinal fluid examination of neurodegenerative diseases

Fumihito Nakano [a,c], Ken Sakushima [a,d,*], Reona Umeki [b], Ichiro Yabe [a], Akira Endoh [b], Hidenao Sasaki [a]

[a] Department of Neurology, Hokkaido University Graduate School of Medicine, Sapporo, Japan
[b] Division of Medical Information Planning, Hokkaido University Hospital, Sapporo, Japan
[c] Department of Neurology, National Hospital Organization Hokkaido Medical Center, Sapporo, Japan
[d] Department of Pharmaceutical and Medical Device Regulatory Science, Hokkaido University Graduate School of Medicine, Sapporo, Japan

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ABSTRACT

Despite recent studies examining the association between neurodegenerative diseases and mitochondrial dysfunction, there are not sufficient data on factors that influence cerebrospinal fluid (CSF) lactate levels. Thus, we investigated factors that affect CSF lactate levels in neurodegenerative diseases. We extracted laboratory findings, including CSF lactate, glucose, and protein levels, and demographic and background information, including age and gender, from the electronic medical records of patients with neurodegenerative diseases in order to explore factors that have an impact CSF lactate levels. These patients had been admitted to our department and underwent a CSF examination between April 2007 and March 2015. Data from 83 patients (average age 64.5 years; 45 males and 38 females) were analyzed. The patients' diagnoses included amyotrophic lateral sclerosis, multiple system atrophy, spinocerebellar degeneration, corticobasal syndrome, Parkinson's disease, and Huntington's disease. CSF lactate levels were higher in patients with a neurodegenerative disease who were aged 65 years and older relative to those who were aged under 65 years ($p < 0.05$), and CSF lactate and glucose levels showed a moderate positive correlation ($r = 0.487$). Age and CSF glucose levels influenced CSF lactate levels even after adjusting for gender, age, CSF protein levels, and CSF glucose levels. When investigating CSF lactate levels in neurodegenerative diseases, it is necessary to consider patients' age and CSF glucose levels.
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1. Introduction

Cerebrospinal fluid (CSF) lactate levels are useful in differential diagnoses of bacterial meningitis and aseptic meningitis, and have been used as a diagnostic tool mainly for infections of the nervous system [1]. Additional diseases with elevated CSF lactate levels include subarachnoid hemorrhage [2], cerebral hypoxia [3], status epilepticus, and congenital metabolic disorder [4]. However, it is important to consider factors that affect CSF lactate levels, as nafronyl administration in patients with senile dementia [5] and a meta-analysis study reported decreased diagnostic accuracy in patients with bacterial meningitis who were administered antibiotics prior to lumbar puncture [6].

Recent studies have examined the association between neurodegenerative diseases, such as Alzheimer's disease (AD), and mitochondrial dysfunction [7,8], and there is evidence of elevated cerebrospinal fluid (CSF) lactate levels in AD [9]. Investigations of CSF lactate levels in neurodegenerative diseases are only beginning to emerge, and there are not sufficient data on factors that influence CSF lactate levels. It is necessary to have prior knowledge of such factors when considering their use as a biomarker for neurodegenerative diseases. Therefore, we investigated factors that affect CSF lactate levels in neurodegenerative diseases.

2. Methods

We retrospectively reviewed the records of patients who were admitted to our department and underwent a CSF examination from April 2007 to March 2015. The diagnosis of each patient was based on a summary report on admission. The summary reports included the diagnosis of each patient, medical history of the disease, results of imaging tests, results of electrophysiological studies, and laboratory findings. We included patients who were diagnosed with or strongly suspected of Parkinson's disease and related disorders (PD), amyotrophic lateral sclerosis (ALS), multiple system atrophy (MSA), spinocerebellar degeneration, corticobasal syndrome, or Huntington's disease. Patients clinically suspected of having one of neurodegenerative diseases were also included, such as a patient with motor neuron symptoms without definitive diagnosis of ALS and a patient with cerebellar ataxia without definitive diagnosis of spinocerebellar degeneration. We excluded patients who suspected diseases other than neuro degenerative diseases and patients who didn't examine a CSF lactate. The results of CSF examinations

* Corresponding author at: Department of Neurology, Hokkaido University Graduate School of Medicine, N15 W7, Kita-ku, Sapporo 060-8638, Japan.
E-mail address: sakusima@med.hokudai.ac.jp (K. Sakushima).

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Table 1
Subject demographics.

	Subjects (n = 83)	
Age, years (SD)	64.5	(13.1)
Under 65 years (%)	37	(44.6)
Sex (female, %)	38	(45.8)
Disease category[a]		
Amyotrophic lateral sclerosis and motor neuron disease (%)	37	(44.6)
Multiple system atrophy (%)	17	(20.5)
Spinocerebellar degeneration (%)	14	(16.9)
Corticobasal syndrome (%)	9	(10.8)
Parkinson's disease and related disorders (%)	5	(6.0)
Huntington's disease (%)	1	(1.2)

[a] Including suspected.

and related laboratory findings were abstracted from the hospital information system of Hokkaido University Hospital.

Descriptive summaries are indicated by the mean and standard deviation (SD) for continuous variables, and frequencies and percentages are used for categorical variables. The chi-square test and Student's *t*-test were used to evaluate differences in frequencies and means, respectively. Pearson's correlation coefficient was used to evaluate associations among variables. Multiple regression analysis was used to find an association between CSF lactate levels and other variables with adjustment for confounding factors. The significance level was set at $p < 0.05$. All statistical analyses were conducted with JMP Pro 11.2.0 (SAS Institute, Inc., Cary, NC).

This study was approved by the Institutional Review Board of Hokkaido University.

3. Results

Patient demographics and diagnoses are summarized in Table 1. Females comprised 45.8% (38/83 cases) of the participants, and the mean age at CSF examination was 64.5 years (range, 21–83). The proportion of patients with ALS and MSA was 44.6% (37/83) and 20.5% (17/83), respectively. Levels of CSF Lactate ranged from 11.1 mg/dl to 20.3 mg/dl and showed no significant difference among disease categories.

Comparisons between patients aged 65 years or more and patients aged under 65 years are shown in Fig. 1. The CSF lactate levels of patients aged 65 years or more were slightly but significantly higher than those of patients aged under 65 years (mean ± standard deviation [SD], 15.5 ± 2.1 mg/dl vs. 14.4 ± 2.1 mg/dl, respectively, $p < 0.05$). In addition, the CSF protein levels of patients aged 65 years or more were higher than those of patients aged under 65 years (mean ± SD, 44.6 ± 13.6 mg/dl vs. 37.3 ± 13.4 mg/dl, respectively, $p < 0.05$). However, there was no significant difference in CSF glucose levels between these two groups.

Correlations between CSF lactate and CSF glucose or protein levels are shown in Fig. 2. CSF lactate levels had a moderate correlation ($r = 0.487$) with CSF glucose levels. In addition, CSF lactate levels had a weak correlation ($r = 0.277$) with CSF protein levels.

Multiple regression analysis revealed that age and CSF glucose levels were independently associated with CSF lactate levels adjusted by sex, CSF white blood cells, and CSF protein levels (Table 2). This multiple regression analysis indicated that higher CSF lactate levels were independently associated with older age and higher CSF glucose levels.

4. Discussion

Our study showed that CSF lactate levels were higher in patients who were aged 65 years and older relative to those who were aged under 65 years, that the correlation between CSF lactate and glucose levels was moderate, and that age and CSF glucose levels were factors that influenced CSF lactate levels even after adjusting for gender, age, CSF protein levels, and CSF glucose levels.

A study of 7614 cases without elevation of cell and protein CSF levels reported a positive correlation between age and CSF lactate levels [10]. Positive correlation is observed in the study of 203 patients who did not have meningitis and underwent lumbar puncture [11], and the study of patients with major depressive disorders [12]. We also observed a correlation between age and CSF lactate levels in the current study, a finding that is consistent with the previous studies.

We found a moderate positive correlation using Pearson's correlation test between CSF lactate and glucose levels in the current study. There are some controversial studies regarding correlation between CSF lactate and glucose levels. Yesavage JA, et al. reported negative and nonsignificant correlation using Spearman rank-order test between CSF lactate and glucose levels [13,14]. Studies examining CSF lactate and glucose levels in patients with lumbar disc herniation and multiple

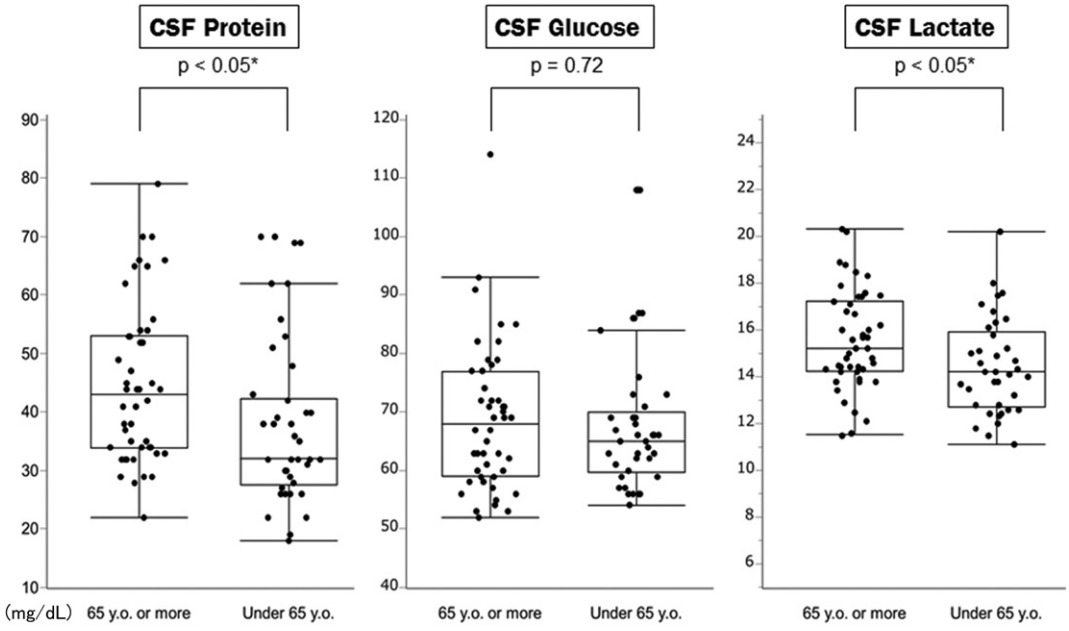

Fig. 1. Comparison between patients aged 65 years or more and those aged <65 years for cerebrospinal fluid (CSF) protein (left), CSF glucose (center), and CSF lactate (right) levels. *Statistically significant ($p < 0.05$).

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