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Original Research Article

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

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Keywords: cerebrospinal fluid, lactate, glucose, age, neurodegenerative disease

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.

Keywords: cerebrospinal fluid, lactate, glucose, age, neurodegenerative disease

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 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 Figure 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 Figure 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 sclerosis showed concurrent changes in CSF lactate and glucose levels [15, 16]. Regenold WT, et al. reported positive correlation between CSF lactate and glucose levels in subjects

consisting of bipolar disorder, schizophrenia, and healthy control [17]. Taking these studies into consideration, the results of the current study support positive correlation between CSF lactate and glucose levels in neurodegenerative diseases.

Mitochondrial dysfunction and hypo-metabolism in central nervous system (CNS) are probably associated with correlations among age, CSF glucose, and CSF lactate. Some genetic forms of neurodegenerative diseases provide causal relationship between mitochondrial dysfunction and disease pathogenesis [7]. Systemic Mitochondrial dysfunction, such as mitochondrial diseases, influences glucose levels and lactate levels in blood. Blood glucose levels affect CSF glucose levels, whereas lactate levels and oxygen saturations don't affect CSF lactate levels [18, 19]. These characteristics of lactate in blood and CSF supports relationship CSF lactate levels between mitochondrial dysfunction in CNS.

In a study comparing 145 patients with AD, 80 healthy controls, and 44 patients with vascular dementia, patients with mild AD had higher CSF lactate levels than those with moderate and severe AD, and patients with AD had higher CSF lactate levels than those with vascular dementia and controls [9], suggesting the possible utility of CSF lactate levels as a biomarker for the diagnosis and prognosis of AD. However, there is no consensus on CSF lactate levels in AD, as exemplified by one study that reported no

elevation of CSF lactate levels in 765 patients with neurodegenerative diseases including progressive supranuclear palsy, MSA, vascular dementia, PD dementia, AD, and motor neuron disease [20].

One limitation of the current study lies in its retrospective design, which resulted in an uneven distribution of neurodegenerative diseases and no cases of AD. As it is possible that AD patients may show greater CSF lactate levels than the other patients examined in the current study, it is necessary to investigate CSF lactate and glucose levels with a group that consists solely of AD patients. In addition, the patients' diagnoses were based on clinical diagnoses available in the medical records, and we did not ensure strict adherence to the diagnostic criteria. However, as there is a report suggesting elevated CSF lactate levels are not disease specific and may be due to changes in metabolism [11], we believe that the results gained from the current study on factors that affect CSF lactate levels in neurodegenerative diseases contribute to the existing literature.

The current study demonstrated that CSF lactate levels were independently correlated with age and CSF glucose levels. When investigating CSF lactate levels in neurodegenerative diseases, it is necessary to consider CSF glucose levels, as well as blood sugar levels that could affect CSF glucose levels and other diseases whose symptoms include variable blood sugar levels, such as diabetes.

The consideration of CSF lactate levels as a biomarker for neurodegenerative diseases has just begun. Age and CSF glucose levels should be taken into consideration upon the use of CSF lactate levels as a biomarker, as the current study showed that they are factors that affect CSF lactate levels.

Conflict of interest

The authors declare no conflicts of interest.

References

[1] S.E. Straus, K.E. Thorpe, J. Holroyd-Leduc, How do I perform a lumbar puncture and analyze the results to diagnose bacterial meningitis?, JAMA 296 (2006) 2012-22.

[2] M. Shimoda, S. Yamada, I. Yamamoto, R. Tsugane, O. Sato, Time course of CSF lactate level in subarachnoid haemorrhage. Correlation with clinical grading and prognosis, Acta Neurochir. 99 (1989) 127-34.

[3] F. Fernandez, A. Verdu, J. Quero, M.C. Ferreiros, E. Daimiel, M.C. Roche, V. Lopez-Martin, Cerebrospinal fluid lactate levels in term infants with perinatal hypoxia, Pediatr. Neurol. 2 (1986) 39-42.

[4] V.P. Calabrese, H.D. Gruemer, K. James, N. Hranowsky, R.J. DeLorenzo, Cerebrospinal fluid lactate levels and prognosis in status epilepticus, Epilepsia 32 (1991) 816-21.

[5] J.A. Yesavage, J.R. Tinklenberg, L.E. Hollister, P.A. Berger, Effect of nafronyl on lactate and pyruvate in the cerebrospinal fluid of patients with senile dementia, J. Am. Geriatr. Soc. 30 (1982) 105-8.

[6] K. Sakushima, Y. Hayashino, T. Kawaguchi, J.L. Jackson, S. Fukuhara, Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from

aseptic meningitis: a meta-analysis, J. Infect. 62 (2011) 255-62.

[7] M.T. Lin, M.F. Beal, Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases, Nature 443(7113) (2006) 787-95.

[8] P.I. Moreira, C. Carvalho, X. Zhu, M.A. Smith, G. Perry, Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology, Biochi. Biophys. Acta 1802 (2010) 2-10.

[9] C. Liguori, A. Stefani, G. Sancesario, G.M. Sancesario, M.G. Marciani, M. Pierantozzi, CSF lactate levels, tau proteins, cognitive decline: a dynamic relationship in Alzheimer's disease, J. Neurol. Neurosurg. Psychiatry (2014) 86:655–659

[10] W.G. Leen, M.A. Willemsen, R.A. Wevers, M.M. Verbeek, Cerebrospinal fluid glucose and lactate: age-specific reference values and implications for clinical practice, PloS one 7 (2012) e42745.

[11] M. Djukic, D. Schulz, H. Schmidt, P. Lange, R. Nau, Cerebrospinal fluid findings in geriatric patients from 2008 to 2011, Z. Gerontol. Geriat. 46 (2013) 353-7.

[12] J.A. Yesavage, C.A. Holman, P.A. Berger, Cerebrospinal fluid lactate levels and aging: findings in normals and patients with major depressive disorders, Gerontology 28 (1982) 377-80.

[13] J. Yesavage, P.A. Berger, Correlation of cerebrospinal fluid lactate with age, Am. J. Psychiatry 137 (1980) 976-7.

[14] J.A. Yesavage, P.A. Berger, Correction to a 1980 article on CSF lactate and age, Am. J. Psychiatry 146 (1989) 118.

[15] M. Garseth, U. Sonnewald, L.R. White, M. Rod, O. Nygaard, J.A. Zwart, Metabolic changes in the cerebrospinal fluid of patients with lumbar disc herniation or spinal stenosis, J. Neurosci. Res. 69 (2002) 692-5.

[16] W.T. Regenold, P. Phatak, M.J. Makley, R.D. Stone, M.A. Kling, Cerebrospinal fluid evidence of increased extra-mitochondrial glucose metabolism implicates mitochondrial dysfunction in multiple sclerosis disease progression, J. Neuro. Sci. 275 (2008) 106-12.

[17] W.T. Regenold, P. Phatak, C.M. Marano, A. Sassan, R.R. Conley, M.A. Kling, Elevated cerebrospinal fluid lactate concentrations in patients with bipolar disorder and schizophrenia: implications for the mitochondrial dysfunction hypothesis, Biol. Psychiatry 65 (2009) 489-94.

[18] J.A. Yesavage, C.A. Holman, F.H. Sarnquist, P.A. Berger, Elevation of cerebrospinal fluid lactate with aging in subjects with normal blood oxygen saturations, J. Gerontol. 37 (1982) 313-5.

[19] J.D. Pryce, P.W. Gant, K.J. Sau, Normal concentrations of lactate, glucose, and protein in cerebrospinal fluid, and the diagnotic implications of abnormal concentrations, Clin. Chem. 16 (1970) 562-5.

[20] S. Jesse, J. Brettschneider, S.D. Sussmuth, B.G. Landwehrmeyer, C.A. von Arnim, A.C. Ludolph, H. Tumani, M. Otto, Summary of cerebrospinal fluid routine parameters in neurodegenerative diseases, J. Neurol. 258 (2011) 1034-41.

Tables and Figures

Figure legends

Figure 1.

Comparison between patients aged 65 years or more and those aged less than 65 years for cerebrospinal (CSF) protein (left), CSF glucose (center), and CSF lactate (right) levels.

*Statistically significant ($p < 0.05$)

Figure 2.

Correlation between cerebrospinal (CSF) lactate and CSF glucose levels (left), and between CSF lactate and CSF protein levels (right). The deep blue line represents regression, and the pale blue area represents the 95% confidence interval of the regression line.

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*	
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)

*Including suspected

Table 2. Interaction between CSF Lactate and Other Variables

	Multiple Regression		
	Coefficient	SE	p-value
Constant	6.628	1.622	
Sex (Female)	-0.435	0.456	0.344
Age	0.042	0.016	< 0.05
CSF Cell Count	0.115	0.286	0.689
CSF Protein	0.017	0.017	0.307
CSF Glucose	0.075	0.017	< 0.01

Figure 1.

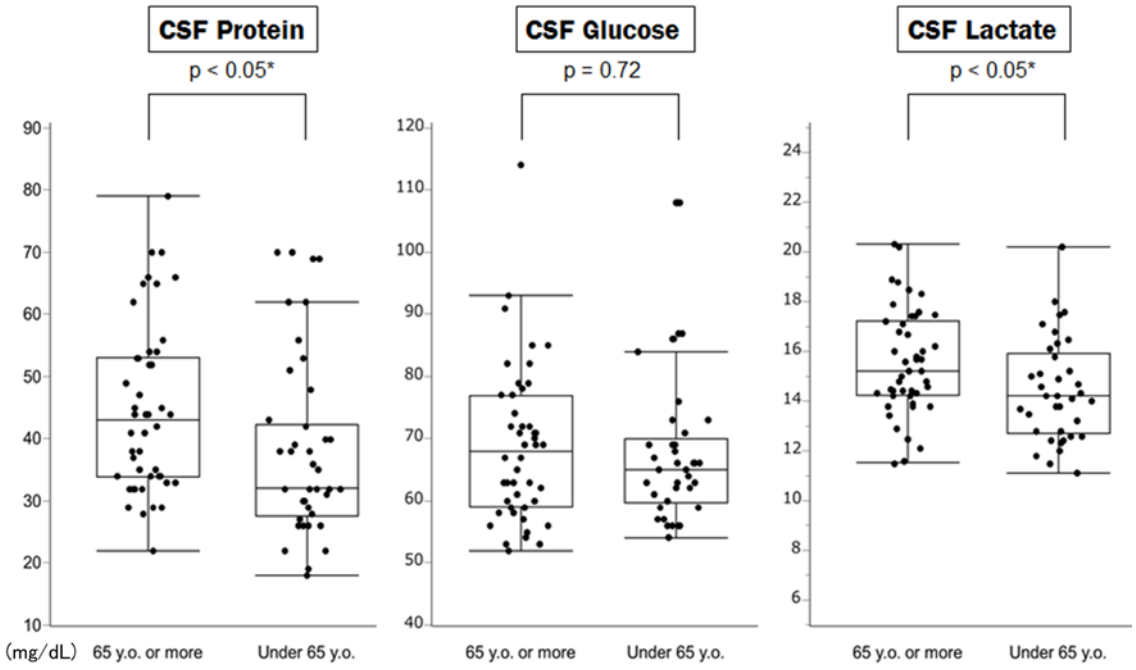
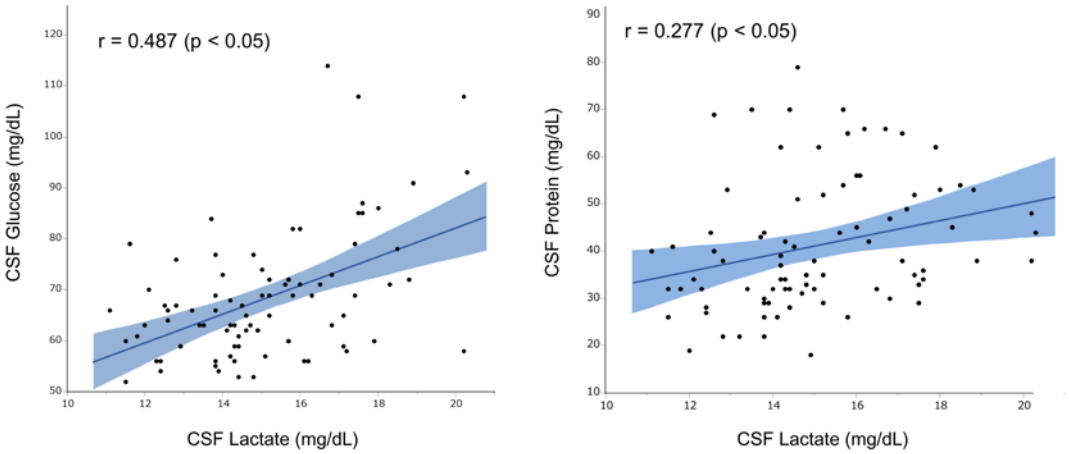

CSF Protein
p < 0.05*
90
80
70
60
50
40
30
20
10
(mg/dL)
65 y.o. or more
Under 65 y.o.
CSF Glucose
p = 0.72
120
110
100
90
80
70
60
50
40
65 y.o. or more
Under 65 y.o.
CSF Lactate
p < 0.05*
24
22
20
18
16
14
12
10
8
6
65 y.o. or more
Under 65 y.o.

Figure 2


r = 0.487 (p < 0.05)
CSF Glucose (mg/dL)
CSF Lactate (mg/dL)
r = 0.277 (p < 0.05)
CSF Protein (mg/dL)
CSF Lactate (mg/dL)