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Usefulness of interleukin 6 levels in the cerebrospinal fluid for the diagnosis of bacterial meningitis☆

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ABSTRACT

Purpose: Interleukin 6 (IL-6) is a proinflammatory cytokine produced during infections. We hypothesized that IL-6 levels in the cerebrospinal fluid (CSF) would be elevated in bacterial meningitis and useful for diagnosing and predicting neurologic outcomes.
Materials and methods: For the differentiation of bacterial meningitis, serum and CSF samples were obtained from patients with an altered level of consciousness. Patients were classified into 3 groups: bacterial meningitis, nonbacterial central nervous system disease, and other site sepsis.
Results: Of the 70 patients included in this study, there were 13 in the bacterial meningitis group, 21 in the nonbacterial central nervous system disease group, and 36 in the other site sepsis group. The CSF IL-6 level was significantly higher in the bacterial meningitis group than in the other 2 groups ($P < .0001$). Of the 5 CSF parameters assessed, CSF IL-6 level exhibited the largest area under the receiver operating characteristic curve (0.962), with a cut-off value of 644 pg/mL (sensitivity, 92.3%; specificity, 89.5%). To examine a potential association between a high CSF level and neurologic outcome, CSF IL-6 levels were divided into 4 quartiles, and each level was compared with the frequency of a good neurologic outcome. The frequency of a good neurologic outcome was significantly lower in the highest CSF IL-6 quartile than in the other 3 quartiles (odds ratio, 0.18; 95% confidence interval, 0.05-0.69; $P = .013$).
Conclusions: Measurement of the CSF IL-6 level is useful for diagnosing bacterial meningitis.

1. Introduction

Although the incidence of bacterial meningitis has declined over the last 10 years due to widespread vaccination, the mortality rate and neurologic outcomes of bacterial meningitis have not yet improved [1]. To improve these, an early and accurate diagnosis is needed [1,2]. Although cerebrospinal fluid (CSF) examination is essential to diagnose bacterial meningitis, it is often difficult to interpret test results, including white blood cell (WBC) count, glucose levels, and CSF protein levels [2]. As these conventional markers are not sufficiently accurate for a diagnosis of meningitis, novel markers have been tested. These novel markers are useful for not only the diagnosis but also the prediction of neurologic outcomes have been tested [2-4].

Interleukin 6 (IL-6) is a proinflammatory cytokine produced during the acute phase response to stimuli such as trauma, surgical insult, or infection [5]. It has been reported that blood IL-6 level is elevated in a variety of diseases related to the inflammatory response [5]. The blood IL-6 level is also positively correlated with the degree of inflammation and severity of sepsis, and it serves as a useful marker for predicting clinical outcomes in such conditions [6]. Furthermore, bacterial infections are reported to be associated with significantly higher blood IL-6 levels than viral pneumonia or urinary tract infections [7].

We thus hypothesized that CSF IL-6 levels would be elevated in bacterial meningitis and served as a useful marker for diagnosis. To test this hypothesis, CSF was sampled by lumbar puncture in critically ill patients needing a differential diagnosis of bacterial meningitis; the sample was assayed for IL-6 to evaluate the sensitivity and specificity of CSF IL-6 level as a diagnostic marker for bacterial meningitis. Furthermore, the association between CSF IL-6 level and neurologic outcomes was examined, as excessive inflammation in the central nervous system (CNS) can cause and seriously impair its function [8].

2. Materials and methods

2.1. Patients

The present study retrospectively analyzed 70 critically ill patients who were admitted to the intensive care unit of Chiba University Hospital (Chiba, Japan) between April 2008, and August 2012 and were subjected to CSF analysis for the diagnosis or differentiation of bacterial meningitis; the CSF analysis included an IL-6 assay. Cerebrospinal fluid samples were collected immediately upon suspicion of bacterial

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Table 1
Type of CNS diseases

Type	n
Bacterial meningitis	13
Nonbacterial CNS diseases	21
Viral meningitis	6
Autoimmune encephalitis	2
Trauma	6
Epilepsy	5
Acute encephalitis	2
Other site sepsis	36

meningitis owing to clinical symptoms, such as fever and/or acute disturbance of consciousness, neck stiffness, and/or seizures. As previously reported [9,10], diagnosis of bacterial meningitis was based on compatible clinical features and one of the following: (*a*) positive CSF culture, (*b*) negative CSF culture but either a positive CSF antigen test or identification of bacteria on Gram staining of the CSF or a positive blood culture, or (*c*) CSF white cell count of 500/mm^3 or more and rapid improvement after antibacterial therapy despite negative CSF and blood culture results. Diagnosis of viral meningitis or encephalitis was based on positive polymerase chain reaction results or antiviral antibodies in the CSF and blood. The final diagnosis of various CNS diseases other than those mentioned above was established by critical care physicians and neurologists based on neurologic findings, hematology, CSF analysis, bacterial culture test, diagnostic imaging including computed tomography and magnetic resonance imaging, brain physiology including electroencephalography, and clinical course. Patients were classified into 3 groups based on the final diagnosis: bacterial meningitis, nonbacterial CNS disease, or other site sepsis [11-13].

The Institutional Research Ethics Board at Chiba University approved this retrospective observational study.

2.2. Measurements

After CSF samples were collected by lumbar puncture, neutrophil counts (cells per cubic millimeter), monocyte counts (cells per cubic millimeter), protein level (milligrams per deciliter), glucose level (milligrams per deciliter), and IL-6 level (picograms per milliliter) in the CSF were immediately determined. We also determined WBC counts (cells per cubic millimeter), C-reactive protein (CRP) levels (milligrams per deciliter), and IL-6 levels (picograms per milliliter) in the blood samples collected at the same time or within the same day of collection of CSF samples. Interleukin 6 levels in the CSF and blood samples were measured using a chemiluminescent enzyme immunoassay system (Lumipulse f, Human IL-6 CLEIA; Fujirebio, Tokyo, Japan,

Table 2
Baseline characteristics of patients

	Bacterial meningitis (n = 13)	Nonbacterial CNS diseases (n = 21)	Other site sepsis (n = 36)	*P*
Age (y)	60 (44-72)	32 (18-63)	67 (49-77)	.0086
Male, n (%)	8 (61.5)	11(52.3)	17 (47.2)	.67
APACHE score	24 (21-29)	18 (17-21)	23 (19-31)	.06
SOFA score	7 (5-11)	8 (4-9)	8 (6-10)	.85
Body temperature	38.8 (38.0-40.0)	38.7 (38.0-39.7)	38.5 (37.7-39.9)	.87
Mean arterial pressure	75 (64-98)	71 (65-86)	63 (54-83)	.0642
Heart rate	120 (108-140)	132 (118-150)	119 (105-140)	.38
Glasgow Coma Scale score	9 (8-10)	8 (6-9)	6 (4-11)	.23
SIRS, n (%)	12 (92.3)	16 (76.2)	34 (94.4)	.0366
Sepsis, n (%)	3 (23.1)	7 (33.3)	11 (30.6)	.30
Severe sepsis, n (%)	8 (61.5)	8 (38.1)	8 (22.2)	.0241
Septic shock, n (%)	1 (7.7)	0 (0)	13 (36.1)	.0021
28-day mortality	0 (0)	0 (0)	2 (5.6)	.37

APACHE indicates Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; SIRS, systemic inflammatory response syndrome.
Data are median (interquartile range) for continuous variables.
P values were calculated using χ^2 or Kruskal-Wallis tests.

Table 3
Blood and CSF data

	Bacterial meningitis (n = 13)	Nonbacterial CNS diseases (n = 21)	Other site sepsis (n = 36)	*P*
Blood				
WBCs, cells/mm^3	17.1 (11.6-24.7)	10.7 (7.7-14.8)	13.4 (7.1-18.1)	.06
CRP, mg/dL	11.9 (5.5-16.2)	3.1 (2.2-5.1)	6.2 (1.9-12.7)	.06
Glucose, mg/dL	140 (112-195)	121 (104-179)	132 (114-175)	.74
IL-6, pg/mL	186 (44-415)	132 (23-238)	389 (81-1697)	.0126
CSF				
Pressure, cm H_2O	19 (6-27)	15 (14-20)	16 (9-25)	.88
Monocytes, cells/mm^3	44 (3-286)	10 (5-28)	3 (0-6)	.0009
Neutrophils, cells/mm^3	1222 (67-2045)	14 (6-150)	3 (1-9)	<.0001
Protein, mg/dL	142 (58-408)	45 (28-83)	31 (22-51)	<.0001
Glucose, mg/dL	54 (16-77)	73 (59-116)	80 (71-97)	.0051
IL-6, pg/mL	6680 (2136-55708)	185 (28-579)	29 (7-92)	<.0001
CSF and blood				
CSF/blood glucose ratio	0.44 (0.097-0.63)	1.34 (0.25-4.35)	0.19 (0.05-0.74)	.0304
CSF/blood IL-6 ratio	138.26 (5.25-376.31)	1.05 (0.25-21.75)	0.05 (0.019-0.120)	<.0001
CSF/blood IL-6 log-fold change	1.85 (0.72-2.57)	0.02 (−0.61-1.34)	−1.29 (−1.73-0.92)	<.0001

CSF/blood IL-6 log-fold change was calculated using formula of $\log_{10}$ CSF IL-6 minus $\log_{10}$ blood IL-6.
Data are median (interquartile range) for continuous variables.
P values were calculated using χ^2 or Kruskal-Wallis tests.

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