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Horai, Yoshiro
Department of Internal Medicine and Rheumatology, Clinical Research Center, National Hospital Organization Kyushu Medical Center

Watanabe, Hideyuki
Department of Internal Medicine and Rheumatology, Clinical Research Center, National Hospital Organization Kyushu Medical Center

Miyamura, Tomoya
Department of Internal Medicine and Rheumatology, Clinical Research Center, National Hospital Organization Kyushu Medical Center

Takahama, Soichiro
Department of Internal Medicine and Rheumatology, Clinical Research Center, National Hospital Organization Kyushu Medical Center

他

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Original Article

Clinical Analysis of Cerebrospinal Fluid Interleukin-6 in Neuropsychiatric Systemic Lupus Erythematosus

Yoshiro Horai, Hideyuki Watanabe, Tomoya Miyamura, Soichiro Takahama, Akie Hirata, Masataka Nakamura, Hitoshi Ando, Rumi Minami, Masahiro Yamamoto and Eiichi Suematsu

Department of Internal Medicine and Rheumatology, Clinical Research Center, National Hospital Organization Kyushu Medical Center, 1-8-1 Jigyohama Chuo-ku, Fukuoka, 810-8563, Japan.

Abstract [Objective] To clarify the clinical usefulness of cerebrospinal fluid (CSF) interleukin-6 (IL-6) measurement in patients with neuropsychiatric systemic lupus erythematosus (NPSLE), we studied CSF IL-6 levels in patients with NPSLE and analyzed the association between CSF IL-6 levels and other clinical findings of NPSLE. [Patients and Methods] We retrospectively analyzed records of 37 patients (33 females and four males) with NPSLE admitted to our hospital between January 2003 and December 2008. [Results] All patients showed neuropsychiatric symptoms. Fourteen patients showed abnormalities in brain magnetic resonance imaging (MRI) and 12 patients had abnormal findings in electroencephalography (EEG). Increased CSF cell counts and elevated levels of CSF IL-6 were found in 11 and 30 patients, respectively. Elevated levels of CSF IL-6 were not statistically correlated with specific abnormalities in the blood analysis, in increased CSF cell counts, and in abnormalities in the brain MRI and EEG. In addition, a group of NPSLE patients positive for antiphospholipid antibodies (aPL) showed lower CSF IL-6 than the patients negative for aPL. [Conclusion] These results indicated that CSF IL-6 might be useful in diagnosis of NPSLE. However, general assessments of patients based on various factors (clinical manifestations, imaging findings and CSF examinations) are also required.

Key words : neuropsychiatric systemic lupus erythematosus, cerebrospinal fluid, interleukin-6

Introduction

Major complications of systemic lupus erythematosus (SLE) include central nervous system (CNS) manifestations. In the diagnosis of the neuropsychiatric symptoms, clinical manifestations, neurological examinations, cerebrospinal fluid (CSF) analysis, brain magnetic resonance imaging (MRI) and electroencephalography (EEG) must be performed. In recent years, abnormal cytokine levels in the cerebrospinal fluid (CSF) have been considered to have an important role in the pathogenesis of NPSLE. CSF levels of inflammatory cytokines, such as interleukin-1 (IL-1)[1], IL-6[1)~5)], IL-8[5)], IL-10[6)], and interferon-α[3)7)], have been studied to elucidate the association between these cytokines and the severity of NPSLE. Among these, IL-6 has been proven to have a strong correlation with NPSLE. IL-6 is an inflammatory cytokine secreted by various immune cells, such as T cells and dendritic cells. This cytokine plays an important role in the immune response to foreign antigens. Furthermore, there have been many studies suggesting that IL-6 is associated with not only the inflammatory response to foreign pathogens, but also with the pathogenesis of various autoimmune diseases and malignancies. In addition, some studies showed that CSF IL-6 levels are useful in the diagnosis of NPSLE[1)~5)]. However, because of a variety of patterns of clinical manifestations of

Corresponding author :
Yoshiro Horai
Tel : + 81-92-852-0700 ; Fax : + 81-92-846-8485
E-mail : yoshirohorai0518@qmed.hosp.go.jp

NPSLE, there are many unresolved issues regarding CSF IL-6 levels and the clinical characteristics of NPSLE. Thus a more intense investigation into the association between CSF IL-6 and the clinical findings of patients with NPSLE seems warranted. In this study, we studied the usefulness of CSF IL-6 testing in the diagnosis and assessment of severity of NPSLE from an analysis of CSF IL-6 levels and symptoms, serological markers, brain MRI and EEG.

Patients and methods

Patients. The study population consisted of 37 patients (33 females and four males) with NPSLE who had been admitted to our hospital between January 2003 and December 2008. All patients fulfilled at least four or more American College of Rheumatology (ACR) criteria for SLE. All patients showed one or more neuropsychiatric symptoms proposed in ACR nomenclature and case definition for NPSLE[8]. Physical symptoms of SLE (skin disorders, oral ulcers, arthritis, serositis, nephritis) were recorded during hospitalization. Neuropsychiatric symptoms were classified based on ACR nomenclature and case definition for NPSLE[8]. Patients with neuropsychiatric symptoms caused by other factors, such as infection, drugs, and metabolic disorders, were excluded. The patients' ages ranged from 17 to 58 years (mean ± SD, 33.7 ± 12.4). The mean disease duration of the patients was 55.2 ± 85.6 months.

Blood samples, CSF analysis, MRI and EEG. Blood specimens were obtained on admission from all patients for immunological analysis. Blood tests were used to measure antinuclear antibody (ANA), anti-double-stranded DNA antibody (anti-dsDNA Ab), anti-Sm antibody, total hemolytic complement (CH_{50}), anti-cardiolipin-IgG antibody (anti-CL-IgG Ab), anti-β_2-glycoprotein-I antibody (anti-β_2 GPIAb), antiphospholipid antibodies (aPL), lupus anticoagulant (LAC) (using diluted Russell's viper venom time), white blood cell count (WBC), hemoglobin and platelet count. CSF samples were also obtained from all patients in this study prior to commencement of immunosuppressive therapy by lumbar puncture according to standard procedures. The CSF samples had cell counts and IL-6 levels measured. The CSF samples were frozen until assayed. The CSF samples were centrifuged and the supernatant was collected. IL-6 levels were measured by chemiluminescent enzyme immunoassay (SRL, Japan). The cut-off value of CSF IL-6 was set at 4.3 pg/ml, recommended by a multicenter retrospective study in Japan approved by the Ministry of Health, Labour and Welfare of the Japanese Government[9]. The patient group with high levels of IL-6 in the CSF ($>$ 4.3 pg/ml) was defined as group 1 (30 patients), and the patient group with low levels of IL-6 in the CSF ($\leqq$ 4.3 pg/ml) was defined as group 2 (7 patients). Brain MRI was performed in all patients, and EEG was performed in 17 patients.

The Chi-square test or Student's t test were used to measure significant differences. Values of $p < 0.05$ were considered to be statistically significant. CSF IL-6 levels were expressed as mean ± SD.

Results

Clinical characteristics of the study population. The physical symptoms of SLE observed were skin disorders in 30 patients, oral ulcers in five, arthritis in 26, serositis in 14 and nephritis in nine patients. Differences in the physical symptoms were not significantly different between group 1 and group 2 (Table 1). All patients showed neuropsychiatric manifestations based on the ACR nomenclature and case definition for NPSLE[8]. The neurologic disorders observed were: aseptic meningitis in one patient, cerebrovascular disease in two, headache in 19, movement disorder in one, myelopathy in one, and seizure disorders in seven patients. The psychiatric disorders observed were : acute confusional state in seven patients, anxiety

Table 1 The association between cerebrospinal fluid (CSF) interleukin-6 (IL-6) levels and clinical manifestations.

	patients with high CSF IL-6 levels (group 1) n=30	patients with low CSF IL-6 levels (group 2) n=7	*p* value
skin disorders	24 (80 %)	6 (86 %)	1.00
oral ulcers	4 (13 %)	1 (14 %)	1.00
arthritis	23 (77 %)	3 (43 %)	0.19
serositis	10 (33 %)	4 (57 %)	0.46
nephritis	8 (27 %)	1 (14 %)	0.84

Table 2 The association between CSF IL-6 levels and neuropsychiatric symptoms.

	group 1 n=30	group 2 n=7	*p* value
neurologic disorders			
aseptic meningitis	1 (3%)	0 (0%)	1.00
cerebrovascular disease	1 (3%)	1 (14%)	0.82
demyelinating syndrome	0 (0%)	0 (0%)	1.00
headache	15 (50%)	4 (57%)	1.00
movement disorder (chorea)	1 (3%)	0 (0%)	1.00
myelopathy	1 (3%)	0 (0%)	1.00
seizure disorders	5 (17%)	2 (29%)	0.85
psychiatric disorders			
acute confusional state	5 (17%)	2 (29%)	0.85
anxiety disorder	0 (0%)	1 (14%)	0.42
cognitive dysfunction	0 (0%)	0 (0%)	1.00
mood disorders	9 (30%)	4 (57%)	0.36
psychosis	1 (3%)	1 (14%)	0.82

Table 3 The association between CSF IL-6 levels and blood analysis.

	group 1 n=30	group 2 n=7	*p* value
ANA-positive	30 (100 %)	7 (100 %)	1.00
anti-dsDNA Ab positive	19 (63 %)	3 (43 %)	0.57
anti-Sm Ab positive	16 (53 %)	1 (14 %)	0.15
low CH_{50}	22 (73 %)	2 (29 %)	0.07
anti-CL-IgG Ab positive	6 (20 %)	0 (0 %)	0.47
anti-β_2GP I Ab	5 (17 %)	0 (0 %)	0.58
LAC positive	5 (17 %)	0 (0 %)	0.58
neutropenia (WBC $<$ 4400/μl)	12 (40 %)	1 (14 %)	0.40
anemia (Hb $<$ 14g/dl in male, $<$ 11.5g/dl in female)	19 (63 %)	6 (86 %)	0.49
low platelet count (plt $<$ 150,000/μl)	11 (37 %)	2 (29 %)	1.00

Abbreviations : ANA, antinuclear antibody ; anti-dsDNA Ab, anti-double-stranded DNA antibody ; CH50, total hemolytic complement ; anti-CL-IgG Ab, anti-cardiolipin-IgG antibody ; anti-β_2GPIAb, anti-β_2-glycoprotein-I antibody ; LAC, lupus anticoagulant ; WBC, white blood cell count ; Hb, hemoglobin ; plt, platelet.

disorder in one, mood disorders in 13 and psychosis in two patients. As for the physical symptoms, there were no significant differences between group 1 and group 2 in the neuropsychiatric symptoms (Table 2).

Analysis of blood samples. The results of blood analysis of all 37 patients were as follows : ANA-positivity in 37 patients, anti-dsDNA Ab in 22, anti-Sm Ab positivity in 17, low CH_{50} in 24, anti-CL-IgG Ab positivity in six, anti-β_2GPIAb positivity in five, LAC positivity in five, neutropenia (WBC count less than 4,400/μl) in 13, anemia (Hb less than 14 g/dl in males, 11.5 g/dl in females) in 25 and low platelet count (platelet count less than 150,000/μl) in 13 patients. There was a tendency toward statistical significance in the relationship high between CSF IL-6 and low CH50 (p = 0.07), but there were no significant correlations with other markers (Table 3).

Analysis of CSF fluid, MRI and EEG. In the 37 samples of CSF, the level of IL-6 was 334.1 ± 497.4 pg/mL. Levels of CSF IL-6 were shown in Fig 1. Increased WBC levels in the CSF (> 5/μl) were observed in 11 patients. The levels of CSF IL-6 in group 1 and group 2 were 398.1 ± 966.9 pg/ml and 2.0 ± 1.2 pg/ml, respectively. Increased numbers of CSF cell counts were found in 11 group 1 patients, but none of the group 2 patients. However, the difference was not statistically significant (Table 4).

In all 37 patients, abnormal MRI findings (hyperintense white matter lesions, enlarged ventricles, lobar atrophy) were seen in 14 patients. In 17 patients in whom EEG examinations were performed, abnormal patterns of the EEG, such as slow waves, sharp waves and spikes were found in 12 patients. There were no significant relationships between high CSF IL-6 levels and high CSF WBC and the findings of MRI (p = 0.46) or EEG (p = 0.84) (Table 4).

The levels of CSF IL-6 in patients with increased CSF WBC levels were 1062.1 ± 2514.4 pg/ml and in patients with normal CSF WBC levels were 10.6 ± 8.5 pg/ml (p = 0.20) (data not shown).

The levels of CSF IL-6 in aPL-positive patients were 15.5 ± 9.1 pg/ml and in aPL-negative patients were 408.1 ± 1590.2 pg/ml (p = 0.19) (data not shown).

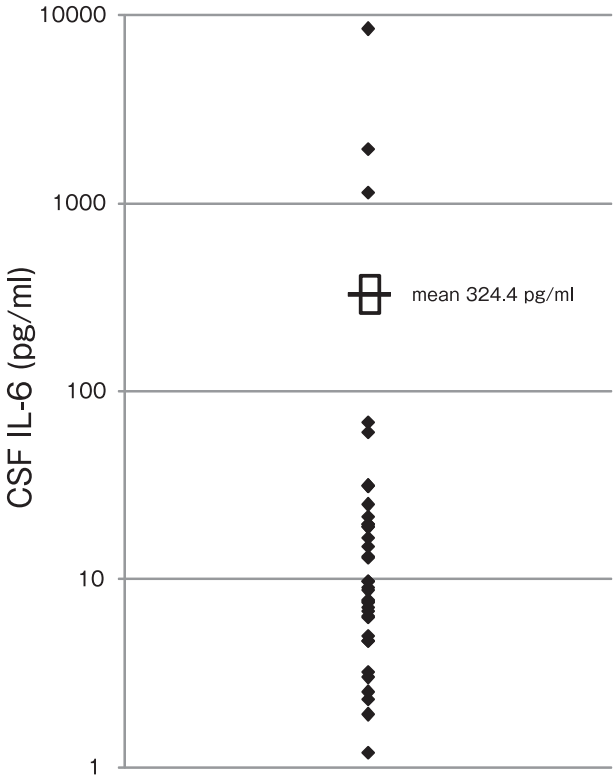

Fig. 1 Levels of interleukin-6 (IL-6) in cerebrospinal fluid (CSF).

Table 4 The association between CSF IL-6 levels and EEG, head MRI and increased numbers of CSF cell counts.

	group 1 n=30	group 2 n=7	*p* value
abnormal patterns of EEG	9 (30%)	3 (43%)	0.84
abnormal MRI findings	10 (33%)	4 (57%)	0.46
Increased numbers of CSF cell counts	11 (37%)	0 (0%)	0.15
CSF IL-6 levels	398.1 ± 966.9 pg/ml	2.0 ± 1.2 pg/ml	

Abbreviations : EEG, electroencephalogram ; MRI, magnetic resonance imaging.

Discussion

Neuropsychiatric symptoms occur in 46～80% of patients with SLE[10)11)]. NPSLE patients show a higher rate of organ damage and have a tendency to require more intensive therapy than SLE patients without neuropsychiatric manifestations[12)]. Therefore, accurate markers to assess NPSLE disease activity are required. Among various biochemical markers, CSF IL-6 is expected to be an independent marker of NPSLE. In this study, CSF IL-6 levels were found to be elevated in 30 of 37 patients. However, the CSF IL-6 levels did not show a statistically significant correlation with any serum immunological markers, although there was a tendency toward a correlation with low CH_{50}. This may imply that high disease activity of SLE showing complement consumption is a potential predictor of neuropsychiatric symptoms.

In the central nervous system, microglia and astrocytes serve as sources of IL-6. Some studies have shown a correlation between CSF levels of IL-6 and symptoms of NPSLE[1～5)]. Although the mechanism of increased production of CSF IL-6 in patients with NPSLE is still not fully understood, it is speculated that CSF IL-6 plays an important role in the pathogenesis of NPSLE. However, CSF levels of IL-6 were not found to be useful as a predictor of particular symptoms, either physical or neuropsychiatric in patients with NPSLE in this study. Because several mechanisms can cause neuropsychiatric symptoms, and clinical manifestations of NPSLE vary among patients, classification of NPSLE using a single marker seems to be problematic.

According to a multicenter retrospective study in Japan approved by the Ministry of Health, Labour and Welfare of the Japanese Government, CSF IL-6 levels are useful for diagnosis of lupus psychosis, with sensitivity and specificity of 87.5% and 92. 3%, respectively, and a recommended cut-off value of 4.3 pg/ml[12]. As high CSF IL-6 levels are not specific for NPSLE, exclusion of other causes, such as infectious meningitis and cerebrovascular diseases, is necessary. In this study, all patients had negative CSF bacterial cultures and no infectious symptoms, and abnormal MRI findings were improved after treatment of SLE. These results indicated that the cause of the neuropsychiatric symptoms was likely to be NPSLE. In addition, there were several NPSLE patients without increased WBC numbers in the CSF, which supported the usefulness of CSF IL-6 measurement in the diagnosis of NPSLE.

The group of patients with increased CSF WBC levels showed a trend toward higher CSF IL-6 levels than the group of patients with normal CSF WBC levels, although the difference was not statistically significant. This suggested that neuropsychiatric symptoms of patients with increased CSF WBC levels might be induced by IL-6 mediated inflammation, not by intracranial embolism and thrombosis. The group of aPL-positive patients showed lower CSF IL-6 levels than the group of aPL-negative patients. It was presumed that the pathogenesis of NPSLE was related to thrombogenesis in the aPL-positive patients, and with vasculitis in the aPL-negative patients.

There are two limitations regarding the present study. First, the study population consisted of only patients with NPSLE. Although elevated CSF IL-6 levels may occur in patients without neuropsychiatric manifestations[2)4)], an analysis of CSF IL-6 of SLE patients without neuropsychiatric manifestations was not done in this study. Another limitation is that CSF samples were obtained only upon the patient's admission. Therefore, the correlation between clinical course of NPSLE patients and levels of CSF IL-6 levels was not fully clarified in this study. However, it is reported that CSF IL-6 levels in patients with NPSLE decreased as they recovered from neuropsychiatric symptoms[2)4)]. Thus CSF IL-6 levels may be a useful marker for not only diagnosis of NPSLE, but also for the evaluation of the clinical course of NPSLE.

There are no specific indicators for NPSLE, and the CSF IL-6 level itself is not necessarily correlated with the severity of NPSLE. The quantification of CSF IL-6 might be useful in the diagnosis and evaluation of NPSLE. However, patient assessments must be based on various factors such as clinical manifestations, image findings and CSF examinations.

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（和文抄録）

Neuropsychiatric systemic lupus erythematosus における髄液 IL-6 の有用性に関する臨床的検討

国立病院機構九州医療センター 膠原病内科・臨床研究センター

寶來吉朗，渡邉秀之，宮村知也，平田明恵，中村真隆，高濱宗一郎，
安藤　仁，南　留美，山本政弘，末松栄一

【目的】全身性エリテマトーデス（SLE）における神経症状はループス腎炎と共に予後を左右する重要な因子である．今回我々は中枢神経病変の評価における髄液 IL-6 の有用性について臨床的検討を行った．【対象及び方法】当院で神経症状合併 SLE と診断した 37 症例（男性 4 例，女性 33 例）の臨床症状，血清免疫学的検査，髄液所見，頭部 MRI 所見及び脳波所見に関して検討を行った．【結果】全例に精神神経症状，12 例に脳波異常，14 例に頭部 MRI 異常，11 例に髄液細胞数増加，30 例に髄液 IL-6 上昇を認めた．患者を髄液 IL-6 上昇群と非上昇群とに分けて比較すると，神経症状（脳血管障害，脱髄性症候，頭痛，運動異常症，脊髄症，痙攣性疾患）及び精神症状（急性昏迷状態，不安症，認識障害，情動障害，精神障害）では両群間に有意差を認めず，脳波及び頭部 MRI の異常所見も両群間に有意差を認めなかったが，髄液 IL-6 上昇群では髄液細胞数が増加する傾向を認めた．一方血清補体価は髄液 IL-6 上昇群で低下していた．更に抗リン脂質抗体陽性群と陰性群に分けて比較すると，陽性群では陰性群より髄液 IL-6 が低い傾向であった．【考察】SLE における神経症状の診断において髄液 IL-6 の値は有用と考えられた．しかしながら髄液 IL-6 非上昇群においても中枢神経症状の合併を認めており，髄液所見，画像診断を含めた総合的な評価が重要と考えられた．