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Original article

# Serum and cerebrospinal fluid cytokine concentrations in subacute sclerosing panencephalitis

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**Abstract**

Subacute sclerosing panencephalitis (SSPE) is a neurodegenerative disease due to persistent measles virus infection. Its immunopathogenesis is unknown. Tumor necrosis factor (TNF)-α, interleukin (IL)-2, IL-6, IL-10 and IL-4 concentrations were measured in cerebrospinal fluid (CSF) and serum samples from 30 SSPE patients and 19 control subjects by cytometric bead array. CSF and serum IFN-γ, IL-12 and IL-18 levels were measured in 18 SSPE patients by ELISA. Serum IL-4 and IL-10 ($p < 0.001$), CSF IL-4 ($p < 0.001$) and IL-6 ($p = 0.049$) concentrations were lower, and serum IL-2 concentrations, higher ($p = 0.001$) in SSPE patients. Serum TNF-α and IL-6, CSF TNF-α, IL-10, and IL-2 concentrations were not different between SSPE and control groups. Serum IFN-γ levels were higher in stage I and II than stage III patients ($p < 0.05$), whereas there was no difference between stages in terms of other cytokines. The levels of Th2-type cytokines: IL-4, IL-6 and IL-10 were suppressed in our SSPE cases. This finding, along with relatively elevated IFN-γ and IL-2 levels, may suggest more active effector T cells compared to regulatory T cells (Treg), especially induced Treg, in early disease. High serum IL-2 concentrations might indicate peripheral Th1 activation. Discrepancies between various reports in the literature should be examined in view of the ages, stage and treatments of the patients studied. The interplay of various cytokines or cellular systems which may vary over time and between patients. Studies of treatment measures favoring the preservation of the early inflammatory response may be of interest in SSPE.
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*Keywords:* Subacute sclerosing panencephalitis; Viral; Immune; Th1; Th2; Cytokines

## 1. Introduction

Subacute sclerosing panencephalitis (SSPE) is a neurodegenerative disease of children and young adults due to persistent measles virus (MV) infection. Factors related to host and virus appear involved in its pathogenesis. Among host factors, the immaturity of the immune system, altered cellular immunity especially in T lymphocytes and T helper (Th) subtypes, presence of high-titer anti-MV antibodies, suppression of some cytokines: IL-12, IFN-γ TNF-α, IL-1β, and elevation of IL-10, IL-6, IFN-β, have been suggested. Most patients with SSPE exhibit decreased MV-specific Th1 cytokine and preserved Th2 cytokine synthesis [1–4]. We measured IFN-γ IL-12, IL-18, TNF-α, IL-2 and IL-6 as markers for Th1-responses and IL-4 and IL-10 as markers for Th2-responses in SSPE in comparison with control subjects.

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## 2. Material and methods

### 2.1. SSPE patients

Paired serum and cerebrospinal fluid (CSF) samples were collected from 48 patients diagnosed with SSPE. The diagnosis was based on three criteria (1) typical clinical manifestations, (2) EEG pattern of high voltage periodic complexes, and (3) measles antibody titers in the serum and CSF detected by complement fixation test ($\geqslant 1/8$) or ELISA (>1.1 IU/ml). All CSF and serum samples were obtained at the time of diagnosis and before treatment, and frozen at −70 °C until tested.

We separated the patients in two groups because of lack of sufficient amount samples. One group of patients ($n = 30$, 23 males, 7 females, 3.5–12 years; median 7 years old) was tested for TNF-α, IL-2, IL-6, IL-10 and IL-4 concentrations in CSF and serum by cytometric bead array. Another group ($n = 18$; 16 males, 2 females, aged 2.5–11 years, median 5 years) was tested for IFN-γ, IL-12 and IL-18 in CSF and serum by sandwich ELISA. All CSF and serum samples were initially analyzed for protein, glucose, and measles antibodies.

The clinical data of the patients were reviewed for clinical staging (stage I to III) and neurological disability index. The course of the disease was classified as subacute, rapidly progressive or slowly progressive according to the rate of change in the neurologic disability index [5].

### 2.2. Control subjects

Control samples for serum and CSF cytokine levels were obtained from 19 Japanese children with non-degenerative neurological disorders such as epilepsy, psychomotor delay, psychosis (10 males and nine females, aged 3–12 years; median 7 years). All had normal CSF cell counts and biochemistry.

The study was approved by the institutional ethics committee of Dr. Sami Ulus Children's Hospital. Informed consent was obtained from parents of SSPE and control patients.

### 2.3. Assays of cytokines

The concentrations of serum and CSF TNF-α, IL-2, IL-4, IL-6, and IL-10 were measured with a cytometric bead array (CBA) kit (BD PharMingen, San Diego, CA) according to the manufacturer's manual, as previously described [6], with modification of the data analysis using GraphPad Prism software (GraphPad Prism Software, San Diego, CA) [7]. The lower detection limits for TNF-α, IL-2, IL-4, IL-6, and IL-10 were 2.8, 2.6, 2.6, 2.5, and 2.8 pg/ml, respectively.

Concentrations of IFN-γ, IL-12 and IL-18 were measured by a sandwich ELISA using the Human IFN-γ ELISA Kit [CytElisa™, Maryland, USA]; Human IL-12 (p70) ELISA kit [CytElisa™, Maryland, USA] and Human IL-18 ELISA Kit [BenderMedSystems, Vienna, Austria]: the sensitivity ranges were: IFN-γ, 15.6–1000 pg/ml; IL-12, 15.6–1000 pg/ml and IL-18, 55–582 pg/ml according to manufacturer's instructions. The inter-assay variations were 10.9% for IFN-γ, 10.9% for IL-12 and 12.9% for IL-18.

Cytokine index was calculated using the following equation:

[Cytokine]CSF/[Cytokine]Serum

: [Albumin]CSF/[Albumin]Serum

### 2.4. Statistical analysis

Data were analyzed using SPSS 9.05 for Microsoft Office. The Mann–Whitney $U$ test was used for comparison between patients, and Wilcoxon Signed Ranks Test, for comparisons between the serum and CSF measurements of each patient. Correlations between variables were calculated using Spearman's and Pearson's Correlation Coefficients.

## 3. Results

Serum IL-4 and IL-10 ($p < 0.001$), CSF IL-4 ($p < 0.001$) and IL-6 ($p = 0.049$) concentrations were lower, and serum IL-2 concentrations, higher ($p = 0.001$) in SSPE than controls. There were no differences in serum TNF-α, IL-6 or CSF IFN-γ, TNF-α, IL-10 and IL-2 concentrations (Table 1). No correlation was observed between cytokine and measles IgG levels in serum or CSF.

Serum IFN-γ levels were higher than CSF IFN-γ ($p < 0.001$) (Table 2). Serum IFN-γ was higher in stage I or II ($81.3 \pm 49.5$) than stage III patients ($42.6 \pm 34$) ($p < 0.05$). The IFN-γ index was higher in patients older than 5 years ($n = 7$) ($178.3 \pm 94.6$) compared to those younger ($n = 11$) ($87.5 \pm 80.4$) ($p < 0.05$). Levels of IL-12 and IL-18 were not associated with any particular feature in terms of age, CSF measles antibody titers, clinical course, stage, neurological disability index (NDI). A rapidly progressive course was found in 10 cases, subacute course in 6, and slow course in 2 patients. Most patients were in stage III ($n = 11$), and others, in stage II ($n = 4$) or I ($n = 2$). There was no difference of cytokine values between patients with progressive course and those with subacute or slow course.

Correlations between serum and CSF levels were examined. Among serum levels, only IFN-γ and IL-12 correlated with each other ($r = 0.48$, $p < 0.05$). Serum IFN-γ correlated with CSF IFN-γ ($r = 0.50$, $p < 0.05$) and CSF IL-18 ($r = 0.47$, $p < 0.05$). Serum IL-12 correlated with CSF IFN-γ, IL-12 and IL-18 ($r = 0.77$ and

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