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Cerebrospinal fluid CXCL13 is a prognostic marker for aseptic meningitis

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ABSTRACT

In exceptional cases, patients with aseptic meningitis eventually develop aseptic meningoencephalitis. To find a candidate marker for the development of aseptic meningoencephalitis in adult patients diagnosed with aseptic meningitis, we compared 12 different cytokines/chemokines in cerebrospinal fluid (CSF) from 5 patients with aseptic meningoencephalitis, 8 patients with aseptic meningitis, and 8 patients with control disease. Only the CXCL13 concentration was significantly elevated in the CSF of the group with aseptic meningoencephalitis compared with the group with aseptic meningitis. Thus, CSF CXCL13 may be a useful marker for predicting the prognosis of aseptic meningitis.

1. Introduction

Aseptic meningitis is usually a self-limiting illness (Jubelt and Miller, 2000). However, in exceptional cases, adult patients initially suffering from the symptoms of aseptic meningitis develop alterations of consciousness and focal neurological deficits. One possible etiology of these cases is post-infectious immune-mediated pathogenesis. For example, patients with aseptic or other meningitis who later developed acute disseminated encephalomyelitis (ADEM) have been reported (Ohnishi et al., 2007; Beleza et al., 2008; Fujiki et al., 2008; Kureshiro et al., 2008; Okada and Yoshioka, 2010; Gołąbek et al., 2011). Although ADEM is a disease characterized by an inflammatory reaction and demyelination of the central nervous system (CNS) in the brain and spinal cord (Menge et al., 2005), Marchioni et al. (2005) reported that site-restricted variants of ADEM, such as encephalitis, have been observed. The other possible etiology of these cases is viral invasion. The differential diagnosis of ADEM from various CNS diseases (e.g., infectious encephalitis and vasculitis) is difficult due to a lack of serologic biomarkers and the extreme variability in the presentation, course, and prognosis of ADEM (Marchioni et al., 2013). Although the pathogenesis of these cases is unknown so far, discriminating aseptic meningitis patients who develop symptoms of CNS parenchyma from those who do not is important. Without early diagnosis and treatment, these aseptic meningoencephalitis cases may have a poor prognosis. In this study, we investigated potential markers for discriminating between aseptic meningitis and aseptic meningoencephalitis during the early phase of illness. We evaluated 10 Th1/Th2 cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12 [p40], IL-13, IL-17A, and IFN-γ) in the cerebrospinal fluid (CSF), most of which had been reported to be elevated in the CSF of aseptic meningitis and ADEM patients (Ichiyama et al., 2002; Ishizu et al., 2006; Mandell et al., 2010). We also evaluated 2 chemokines (IL-8 and CXCL13) in the CSF that were recently reported as candidate markers of intrathecal inflammation (Bielekova et al., 2012; Kowarik et al., 2012; Alvarez et al., 2013).

2. Materials and methods

2.1. Patients

The medical records of patients treated at Tohoku Pharmaceutical University Hospital and Tohoku University Hospital between 2004 and 2011 were retrospectively assessed. CSF samples from 5 patients with aseptic meningitis who developed alterations of consciousness and focal neurological deficits, from 8 patients with aseptic meningitis, and from 8 patients with non-inflammatory neurological disorders as a control group were analyzed. We defined the cases with aseptic meningitis who developed alterations of consciousness (Glasgow coma scale <14) and focal neurological deficits as the cases with aseptic meningoencephalitis in this study. Of the 5 patients with aseptic meningoencephalitis, 3 were diagnosed as aseptic meningitis at admission and later

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developed alterations of consciousness and focal neurological deficits (cases 1–3). The other 2 patients suffered from continuous headaches and fever for a week before admission, and neck stiffness, alterations of consciousness and focal neurological deficits were recognized at admission (cases 4 and 5). Of the 5 patients with aseptic meningoencephalitis, CSF samples from 4 patients (cases 1, 2, 4, and 5) were collected during the acute phase (within approximately 2 weeks), and CSF samples from another patient (case 3) were collected during the subacute phase (within approximately 6 weeks). All CSF samples were collected before steroid therapy. CSF samples from 4 patients (cases 1, 2, 4, and 5) were collected before the administration of acyclovir. The CSF sample of another patient (case 3) was collected after the administration of acyclovir. Multiple causative viruses were surveyed in each patient. CSF DNA (PCR) for Herpes simplex virus (HSV) and CSF IgM and IgG against HSV, varicella zoster virus (VZV), and cytomegalovirus (CMV) were surveyed in all 5 aseptic meningoencephalitis patients. The diagnosis of aseptic meningitis was based on clinical features and CSF findings. All CSF samples of aseptic meningitis were collected during the acute phase. Of the 8 cases of aseptic meningitis, 2 were caused by varicella zoster virus, and 2 were caused by mumps virus. The causative virus in the other 4 cases was unknown. A patient with meningitis-retention syndrome was excluded from the aseptic meningitis group. Patients with malignant neoplasms, vasculitis, neuro-Behcet disease, collagen disease, and other autoimmune diseases, including Hashimoto's encephalopathy, viral encephalitis, and metabolic diseases were excluded. Patients with early symptoms of psychosis or seizure were excluded to avoid including limbic encephalitis.

The CSF cell count and protein content data were available for all patients. We compared the CSF cell counts and amount of CSF protein among the 5 aseptic meningoencephalitis patients, 8 aseptic meningitis patients, and 8 controls. IgG and albumin levels in the serum and CSF, measured by nephelometry, were available in 4 aseptic meningoencephalitis patients (cases 1 and 3–5), 5 aseptic meningitis patients, and 3 controls. We compared the CSF albumin, CSF IgG, Qalb, and IgG indices of the patients. A disturbance of the blood–brain barrier (BBB) was diagnosed if the ratio of albumin in CSF and serum (Qalb) exceeded 0.009 (Bowman et al., 2007).

2.2. Cytokine/chemokine multiplex assay

The concentrations of CSF cytokines/chemokines were measured with the use of a Procarta® Immunoassay Kit, according to the manufacturer's instructions (Panomics, CA, USA). After incubation with Ab-conjugated beads, detection Abs, and streptavidin–PE complexes, CSF samples that were diluted 4 times with dilution buffer were run on a Bio-Plex instrument (Bio-Rad). The concentrations of the following cytokines and chemokines were evaluated: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p40), IL-13, IL-17A, IFN-γ, and CXCL13.

2.3. Statistical analysis

We used the Kruskal–Wallis H-test and Mann–Whitney's *U*-test with the Bonferroni correction for comparison and Spearman's correlation for the correlation and regression analyses. $p < 0.05$ was accepted as indicative of statistical significance.

3. Results

3.1. Patients

There was no significant difference in age and sex among the 3 groups that were evaluated (i.e., aseptic meningoencephalitis patients, aseptic meningitis patients, and controls) (Table 1). The number of days from the onset of disease to CSF sample collection was significantly longer in aseptic meningoencephalitis patients than in the controls ($p = 0.043$). However, the number of days from the onset to CSF sample collection was not significantly different between the aseptic meningoencephalitis patients and aseptic meningitis patients and between the aseptic meningitis patients and controls. The profile of the patients with aseptic meningoencephalitis is summarized in Table 2. Steroid therapy was administered in 4 patients (cases 1, 2, 4, and 5) and was effective in all patients. Intravenous immunoglobulin (IVIg) was also administered only to case 1, who needed intensive care including mechanical ventilation during the acute phase. Because

Table 1
Comparison of laboratory parameters between aseptic meningitis and aseptic meningoencephalitis (mean ± SD).

	Control (n = 8)	Aseptic meningitis (n = 8)	Aseptic meningoencephalitis (n = 5)	p-Value
Age	27.25 ± 10.81	22.37 ± 4.50	41.2 ± 12.96	NS
Sex	Male 2, female 6	Male 5, female 3	Male 3, female 2	NS
Days from the onset to CSF collection (days)	2 ± 1.92	2.752 ± 2.81	14 ± 15.95	NS
CSF cells (/μl)	1.50 ± 1.51	186.62 ± 241.12	84.6 ± 79.46	NS
CSF protein (mg/dl)	28.50 ± 7.89	74.37 ± 42.98	136.8 ± 64.55	NS
CSF IL-1b (pg/ml)	0.00 ± 0.00	1.72 ± 2.69	1.45 ± 2.04	NS
CSF IL-2 (pg/ml)	0.00 ± 0.00	1.17 ± 1.96	0.94 ± 1.40	NS
CSF IL-4 (pg/ml)	0.76 ± 1.44	30.13 ± 40.97	16.02 ± 17.14	NS
CSF IL-5 (pg/ml)	0.00 ± 0.00	8.08 ± 10.04	23.13 ± 21.41	NS
CSF IL-6 (pg/ml)	32.34 ± 65.37	784.97 ± 1450.13	215.83 ± 226.06	NS
CSF IL-8 (pg/ml)	25.64 ± 19.04	803.21 ± 1223.09	296.75 ± 298.72	NS
CSF IL-10 (pg/ml)	0.24 ± 0.68	74.18 ± 158.12	8.24 ± 7.56	NS
CSF IL-12 (p40) (pg/ml)	0.00 ± 0.00	9.32 ± 9.60	24.63 ± 6.09	NS
CSF IL-13 (pg/ml)	0.00 ± 0.00	2.22 ± 4.12	7.66 ± 9.08	NS
CSF IL-17 (pg/ml)	0.00 ± 0.00	1.10 ± 3.13	1.69 ± 3.78	NS
CSF IFN-ϒ (pg/ml)	0.27 ± 0.77	74.24 ± 103.41	118.21 ± 138.13	NS
CSF CXCL13 (pg/ml)	0.00 ± 0.00	33.73 ± 40.77	324.07 ± 226.01	p = 0.0233
	Control (n = 3)	Aseptic meningitis (n = 5)	Aseptic meningoencephalitis (n = 4)	p-Value
CSF ALB (mg/dl)	17.30 ± 5.83	40.06 ± 22.35	107.83 ± 66.93	NS
CSF IgG (mg/dl)	2.20 ± 1.058	4.92 ± 2.407	13.65 ± 7.097	NS
Qalb	0.0037 ± 0.0012	0.0092 ± 0.0055	0.0268 ± 0.014	NS
IgG index	0.4917 ± 0.0144	0.472 ± 0.067	0.5225 ± 0.0359	NS

A comparison analysis was performed between patients with aseptic meningitis and those with aseptic meningoencephalitis.
$p < 0.05$ was accepted as indicative of statistical significance.
NS, not significant.

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