Adult Meningism and Viral Meningitis, 1997-2004: Clinical Data and Cerebrospinal Fluid Cytokines

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Abstract

Objective Although meningism manifesting acute headache has been observed to be associated with common viral and bacterial infections, its definition and pathogenesis have not been clarified. Clinical findings and cerebrospinal fluid (CSF) cytokines in adult patients with meningism were investigated and compared with those in viral meningitis.

Patients and Methods Among the adult inpatients in our hospital from 1997 to 2004, 5 with meningism and 17 with viral meningitis were identified according to the criteria described in this study, and their clinical data were analyzed. In the CSF samples of the 5 patients with meningism and the 17 with viral meningitis, the concentrations of interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), IL-4, IL-6, and IL-10 were determined using a cytometric bead array.

Results The five patients with meningism all showed fever and meningeal signs such as severe headache and nuchal stiffness without CSF pleocytosis (<5 cells/mm³). Four patients were associated with herpetic Kaposi’s eczema, herpes simplex, or herpes zoster, and all five patients had favorable outcomes. The levels of all CSF cytokines in patients with meningism were below normal values, whereas IFN-γ and IL-6 in patients with viral meningitis were moderately elevated.

Conclusion The normal cytokine levels in meningism may possibly reflect the lack of direct viral infection and may be helpful in differentiating both meningism and viral meningitis at an early stage.

Key words: meningism, viral meningitis, headache, cerebrospinal fluid, cytokine

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Introduction

Meningism presents with acute headache and signs of meningeal irritation without cerebrospinal fluid (CSF) pleocytosis, and it is sometimes associated with common viral or bacterial infections such as influenza, chickenpox, or streptococcus pharyngitis. Acute hypotonicity of the patient’s serum, an increased formation of CSF, and fever-related headache have been considered as possible causes (1–4). Little information is available, however, regarding the definition and pathophysiology of adult meningism. Meanwhile, viral meningitis is characterized by fever, meningeal irritation signs such as headache, vomiting, and nuchal stiffness, CSF pleocytosis, increased protein content, and normal glucose concentrations. Recent viral studies, including polymerase chain reaction (PCR), have been able to identify the causative agents from CSF samples in patients (5–7).

In the present study, we analyzed clinical data, including CSF findings, viral studies, and CSF cytokines for 22 adult inpatients, 5 with meningism and 17 with viral meningitis.

Patients and Methods

We examined adult inpatients with meningism and viral meningitis from 1997 to 2004 at Kurume University Hospi-
The clinical data were analyzed for each patient. The diagnosis of meningism and viral meningitis (1, 2, 5, 6) was determined according to the following criteria: meningism was defined as patients with acute headache and meningeal signs in the absence of CSF pleocytosis (i.e. cells were under 5 per mm$^3$); in contrast, viral meningitis was defined as being characterized by acute onset, fever, meningeal irritation signs, CSF pleocytosis, increases in protein content, and normal glucose levels. Regarding etiology, PCR, and serology assays for herpes simplex virus (HSV) 1 and 2, varicella-zoster virus (VZV), influenza virus, and other viruses were applied by nested PCR or reverse transcript (RT)-PCR for the CSF samples at the acute stage and by enzyme-linked immunosorbent assay (ELISA, or EIA) for the serum and CSF during the acute to convalescent stages.

Determination of cytokine concentrations: With informed consent, CSF samples were taken within 2 weeks after onset (mean: 5 days) of diseases from 5 patients with meningism and from 17 with viral meningitis; the samples were stored at -80°C. The concentrations of interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin -2 (IL-2), IL-4, IL-6, and IL-10 in the CSF were determined with a cytometric bead array kit (BD PharMingen, San Diego, CA). The detection limits were <46.6 pg/ml for IFN-γ, <6.2 pg/ml for TNF-α, <4.6 pg/ml for IL-2, <11.6 pg/ml for IL-4, <9.7 pg/ml for IL-6, and <6.1 pg/ml for IL-10, respectively. Data are presented as means±SD. The statistical significance was evaluated using the Wilcoxon and Siegel-Tukey two-sample rank tests (8, 9). P values of less than 0.05 were considered significant.

Results

Clinical data (Tables 1, 2)

Five patients with meningism were found; their mean age was 41 years (range 22-66 years), with a 4 : 1 male : female ratio. All patients showed similar acute meningeal symptoms such as severe headache and fever for several days. Meningeal signs such as nuchal stiffness were mild; in Patients 3 and 4 the nuchal stiffness was not clear, but they complained of nausea or photophobia. Four patients were associated with viral infections. Patients 1 and 2 were complicated with generalized herpetic Kaposi’s eczema following atopic dermatitis, with both patients showing disseminated herpetic eruptions including the face and body. Patient 3 had a strange headache with herpes zoster, a throbbing headache on the left side that occurred several days after left abdominal herpes zoster, and Patient 4 had an acute headache and nausea following oral herpes simplex. Patient 5 had an acute migraine-like headache in the frontal region with acute pharyngitis, and showed no serum hypotonicity.

Regarding CSF pressure, patients with meningism showed a slight increase (n=4, mean=185 mmH2O) compared with those with viral meningitis (n=17, mean=154.5). None of the patients with meningism exhibited CSF pleocytosis (mean=2.7 /mm$^3$); in addition, the protein content (mean=32.4 mg/dl) and glucose concentrations were normal. Ten days after the initial CSF testing, the 2nd CSF in Patient 3 again revealed normal findings. In all patients, plain head CT revealed no apparent abnormalities. Acyclovir was given for Patients 1-4, and antibiotics were used to treat Patient 5. The mean number of hospitalized days was 8.5, and all five patients had favorable outcomes.

In the 17 patients with viral meningitis, the mean age was 32.2 years, male : female 10 : 7, and all patients revealed moderate CSF pleocytosis with increased protein content. In a few patients at the acute stage, CT abnormalities suggesting increased brain pressure were observed. Acyclovir with antibiotics or a drug to reduce brain pressure was given, and good outcomes were obtained in these cases, except for three recurrent cases. The number of hospitalized days averaged 16.2.

In the 5 patients with meningism, HSV 1 and 2, VZV genomes were not detected in the CSF samples by nested PCR for the CSF samples in patients 1-4; in Patient 1, serum HSV type-specific EIA IgG antibody for HSV 1 was positive, and in Patient 2, HSV 1 was identified for the HSV strain isolated from his salivation, and for Patient 4, HSV 2 was positive for the smear taken from his perioral vesicles, while a high titer of 1 : 64 was observed for VZV in Patient 3. In Patient 5, no causative agent was identified.

Of the 17 patients with viral meningitis, 4 with herpetic stomatitis and genital herpes, 2 with HSV 1, and 2 with HSV 2 were confirmed by PCR or serology; for 4 patients, 1 case of influenza A and 3 of influenza B were diagnosed by serum hemagglutination inhibition (HI) antibody changes; however, in 4 patients influenza virus was not detected by CSF RT-PCR. One case each of coxsackie A7, mumps, and Epstein-Barr virus was diagnosed by serologic testing.
Table 2. Clinical Characteristics of 5 Patients with Meningism

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
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<tbody>
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<td>Age (yrs)/Sex</td>
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<td>26/M</td>
<td>66/F</td>
<td>55/M</td>
<td>22/F</td>
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<tr>
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<tr>
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<tr>
<td>Headache</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
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<td>Nausea</td>
<td>-</td>
<td>-</td>
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<td>+</td>
<td>+</td>
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<tr>
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<td>Complications</td>
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<td>Pathogen</td>
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<td>Type-specific ELISA or EIA</td>
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<tr>
<td>HSV 1 1.38 (+)</td>
<td>HSV 1 0.47 (+)</td>
<td>HSV 1 IgM 1.36 (+)</td>
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<tr>
<td>HSV 2 2.07 (+)</td>
<td>HSV 2 0.29 (+)</td>
<td>HSV IgG 83.8 (+)</td>
<td>HSV 2 5.67 (+)</td>
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<td></td>
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<tr>
<td>CSF HSV PCR</td>
<td>(-)</td>
<td>(-)</td>
<td>VZV PCR (-)</td>
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<td>CSF findings</td>
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<td>Cells (/mm³)</td>
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<td>1.7</td>
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<td>Glucose (mg/dl)</td>
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<td>47</td>
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<td>IL-6 (pg/ml)</td>
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<td>5</td>
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<tr>
<td>IFN-γ (pg/ml)</td>
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<td>2.8</td>
<td>8.6</td>
<td>7.1</td>
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</table>

M, Male; F, Female; HSV, herpes simplex virus; VZV, varicella-zoster virus; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; PCR, polymerase chain reaction; CSF, cerebrospinal fluid; nd, not done; IL-6, interleukin-6; IFN-γ, interferon-γ.

Figure 1. Cytokines in the cerebrospinal fluid of patients with meningism (A, n=5) and viral meningitis (B, n=17). The levels of all CSF cytokines in patients with meningism were below normal values, whereas IFN-γ and IL-6 in patients with viral meningitis were moderately elevated. * Siegel-Tukey test, ** Wilcoxon test, IFN-γ, interferon-γ; IL-6, interleukin-6.

Recurrent patients with viral meningitis; three recurrent cases of viral meningitis were identified. A 47-year-old female, who had 3 recurrent attacks, was confirmed as having HSV 2 Mollaret’s meningitis by PCR study (10). Another patient, a 47-year-old male, appeared to have EBV meningitis due to the high EBV antibody titer. In these three patients, a throbbing headache tended to precede the time of recurrence rather than inflammatory symptoms such as fever.

CSF cytokines (Fig. 1)

The levels of CSF cytokines are presented as means±SD. The levels of all CSF cytokines in patients with meningism (n=5) were below normal values. The levels for meningism were 7.6±0.7 pg/ml for IFN-γ and 4.7±1.5 pg/ml for IL-6, while those for viral meningitis (n=17) were 784.1±1,613 pg/ml for IFN-γ (two-sided p=0.019 by Siegel-Tukey test) and 372.7±518.7 pg/ml for IL-6 (two-sided p=0.04 by Wilcoxon test). In viral meningitis, the levels of CSF IL-2 and IL-10 were slightly increased to 12.2±345.9 pg/ml and 27.9±47 pg/ml, but the statistical differences with those in meningism were not significant, meanwhile the levels of TNF-α and IL-2 were below the detection limits.

Regarding the statistical analysis in IFN-γ, because both groups included several cases with below and upper detection limits no test for testing shift parameters was considered reasonable, and we employed the Siegel-Tukey test. In contrast with IL-6, because of the few detection limits in only one group, the Wilcoxon test for testing shift parameters was reasonably applied.

Discussion

Adult meningism has rarely been referred to in recent literature. The term has been applied to patients with acute headache and signs of meningeal irritation in the absence of CSF pleocytosis (1, 2). Five patients with meningism were identified; in two patients meningeal signs such as nuchal stiffness were not clear, but nausea or photophobia was present. The five adult patients presented with meningism associated with generalized herpetic Kaposi’s eczema, herpes zoster, oral herpes simplex, and acute pharyngitis. Furthermore, various headaches attributed to viral and bacterial infections, headache with testicular pain in mumps infection, and migraine-like headache preceding herpetic encephalitis have been reported (3, 4, 11, 12). In the early stages, however, the differential diagnosis between meningism and headache in viral meningitis or encephalitis is not always easy. CSF testing appears to be a first step to differentiating these disorders.

Regarding the pathogenesis of meningism, acute hypoton-
licity of the patient’s serum, inappropriate secretion of antidiuretic hormone, and an increased formation of CSF have been discussed (1,2). In addition, severe headache may occur in response to fever-related substances or direct invasion of infectious agents to the brainstem nuclei such as locus coeruleus and trigeminal nuclei (3,4). For our patients, a definitive cause has not been identified.

In our study, the levels of all CSF cytokines in patients with meningism were within normal values, while IFN-γ and IL-6 in patients with viral meningitis were moderately elevated. IFN-γ or IL-6 is often elevated in viral meningitis and encephalitis, but not in postinfectious encephalitis or acute disseminated encephalomyelitis (13-15). These cytokine changes may correspond with those occurring in response to viral invasion into the meningeal space. Ichiyama et al (16) have reported unchanged cytokine levels in child febrile seizures, but elevated levels in acute encephalitis/encephalopathy. In contrast, Sato et al (7) have reported cytokine changes in CSF samples without pleocytosis in the acute stage of enteroviral meningitis. It seems that child epidemic meningitis includes a few meningitis types together with the majority of meningitis types.

The results in our adult patients with meningism may suggest a lack of direct infection of the meningeal space. In addition, the cytokine data may be helpful in differentiating meningism and viral meningitis at an early stage.

In viral meningitis in our study, one patient with HSV 2 Mollaret’s meningitis complained of a migraine-like headache during the second and third attacks, and recurrence was suspected, though it was eventually ruled out due to the lack of CSF pleocytosis. At the same time, CSF cytokine changes were not found. Accordingly, CSF cytokine data may also be a marker of either viral recurrence or merely headache in HSV 2 Mollaret’s meningitis.

In conclusion, clinical data, including CSF cytokines, were examined for 5 adult inpatients with meningism and 17 with viral meningitis for the past 7 years. The levels of all CSF cytokines in patients with meningism were below normal values, whereas IFN-γ and IL-6 in patients with viral meningitis were moderately increased. Thus, CSF cytokines may be useful in differentiating meningism and viral meningitis at the acute stage. Because of the few patients with meningism in this study, however, further studies will be necessary to clarify the pathogenesis and pathophysiology.

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References