Inflammatory Cytokines Locally Elevated in Chronic Subdural Haematoma

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Summary

The involvement of inflammation in the development and propagation of chronic subdural haematoma (CSH) was investigated by measuring the levels of inflammatory cytokines (tumour necrosis factor [TNF]α, interleukin [IL]-1β, IL-6, and IL-8). Peripheral venous blood and subdural fluid were obtained at the time of burr hole surgery from 34 patients with CSH and from 9 with subdural effusion. The levels of the inflammatory cytokines were analysed by enzyme-linked immunosorbent assay. The blood levels of TNFα, IL-1β, IL-6, and IL-8 in both CSH and subdural effusion groups were almost within the range of normal subjects, and no differences were observed between the two groups. IL-6 and IL-8 in the subdural fluid were much higher than in the blood of both groups, and the levels in CSH patients were significantly higher (10 times) than in subdural effusion patients. Local elevation of inflammatory cytokines in the subdural space of both CSH and subdural effusion without systemic change suggests the presence of local inflammation in the two diseases. The same behavioural patterns of cytokines for these and higher levels of cytokines in the CSH also suggest that inflammatory cytokines may be involved in the continuous development from subdural effusion to CSH and propagation of CSH.

Keywords: Chronic subdural haematoma; cytokines; subdural effusion; inflammation.

Introduction

Chronic subdural haematoma (CSH) was originally described as an inflammatory disease under the name “pachymeningitis haemorrhagica interna” [33]. Several indications of inflammation, such as proliferation of fibroblasts, immature capillaries, and collagen fibrils, and infiltration of inflammatory cells have been described in the outer membrane of CSH [27, 32, 38]. The causative factor of CSH is trauma, not inflammation [32]. However, the current concept of “inflammation” has expanded from infection or tissue repair to include head injury, cerebral infarction, sub-arachnoid haemorrhage, degenerative diseases, and brain tumours [11, 15, 17, 18, 23, 31, 35, 36]. Therefore, inflammatory reaction is also likely to occur in CSH following head injury.

Recently, interest has been focused on local fibrinolytic activity in the outer membrane of CSH [3, 20]. Immature capillaries in the outer membrane produce tissue type plasminogen activator, which might cause local hyperfibrinolytic activity and resultant bleeding [3]. The vasculature also has high permeability to blood components and causes enlargement of CSH [6, 37]. Immature capillaries are an ubiquitous phenomenon during angiogenesis in inflammation, and are usually accompanied by hyperfibrinolytic activity and increased permeability like that in the outer membrane [7, 8]. Therefore, CSH can be studied as a type of inflammatory phenomenon.

Neurological imaging has shown that CSH may develop following subdural effusion [13, 22], but no factor promoting CSH from subdural effusion has been identified. Inflammatory cytokines (tumour necrosis factor [TNF]α, interleukin [IL]-1β, IL-6, and IL-8) are considered to be involved in the inflammatory reaction and are used as indicators in various neurological disorders [12, 17, 18, 25, 29, 35, 36]. However, the levels of inflammatory cytokines have never been measured in the subdural fluid of patients with CSH and/or subdural effusion.

This study analysed these indicators of inflammation in the blood and subdural fluid of patients with CSH or subdural effusion in order to investigate the involvement of inflammation in the mechanism of initiation and propagation of CSH following subdural effusion.
Table 1. Inflammatory Cytokines in Blood and Subdural Fluid

<table>
<thead>
<tr>
<th></th>
<th>TNFα (pg/ml)</th>
<th>IL-1β (pg/ml)</th>
<th>IL-6 (pg/ml)</th>
<th>IL-8 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>blood</td>
<td>&lt;20</td>
<td>&lt;2</td>
<td>&lt;10</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Patients with CSH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>blood</td>
<td>3.5 ± 0.5</td>
<td>&lt;2</td>
<td>4.8 ± 1.5</td>
<td>7.0 ± 5.6</td>
</tr>
<tr>
<td>subdural fluid</td>
<td>41.1 ± 8.8a</td>
<td>&lt;2</td>
<td>2549 ± 395.9b-d</td>
<td>1597.6 ± 451.5b-d</td>
</tr>
<tr>
<td>Patients with subdural effusion</td>
<td>&lt;3</td>
<td>&lt;2</td>
<td>5.0 ± 2.7</td>
<td>&lt;3</td>
</tr>
<tr>
<td>subdural fluid</td>
<td>7.8 ± 4.4</td>
<td>&lt;2</td>
<td>256.3 ± 93.7c</td>
<td>129.5 ± 51.9c</td>
</tr>
</tbody>
</table>

*Values are means ± standard errors.

TNFα tumour necrosis factor-α, IL-1β interleukin-1β, IL-6 interleukin-6, IL-8 interleukin-8.

a p < 0.05, b p < 0.0001 vs. value in the blood of patients with CSH.
b p < 0.05 vs. value in the blood of patients with subdural effusion.
c p < 0.0001 vs. value in the subdural fluid of patients with subdural effusion.

Patients and Methods

Thirty-four patients, 22 males and 12 females aged from 43 to 84 years (mean 73.8 years) with CSH, and nine patients, 6 males and 3 females aged from 65 to 76 years (mean 71.1 years) with subdural effusion, were studied. The diagnoses were based on X-ray computed tomography (X-CT) and operative findings. CSH was defined as a subdural fluid collection with higher X-CT density than cerebrospinal fluid (CSF), an apparent outer membrane beneath the dura mater, and content including blood cells or their debris. Subdural effusion was defined as a liquid collection with almost the same X-CT density as CSF, a thin or no outer membrane, and clear to xanthochromic contents without blood cells. The primary cause of CSH was head injury or unknown. Subdural effusion was caused by trauma in 3 patients and intracranial surgery in 6 (patients with malignant tumour were excluded).

Samples of subdural fluid and venous blood were obtained at the time of burr hole irrigation surgery under local anaesthesia. Samples were centrifuged at 1700 g (3000 rpm) for 10 minutes immediately, and the supernatant plasma was stored in sealed plastic tubes (NALGEN® Cryogenic vials, Nalge Company, Rochester, NY) at −80°C until analysis. Inflammatory cytokines were assayed using the following enzyme-linked immunosorbent assay kits: TNFα (MEDGENIX DIAGNOSTICA, Brussels, Belgium), IL-1β (Ohtsuka, Tokyo, Japan), IL-6 (Toray-Fuji Bionics Inc., Tokyo, Japan), IL-8 (Toray-Fuji Bionics Inc.).

CSH patients were classified into two types according to the X-CT pattern: the layering type consisting of an upper hypodense and lower hyperdense portion, which is reported to be active and recurrent [20, 26 and others]. Ten of the 34 patients were classified as the layering type.

The levels of inflammatory cytokines in the blood were compared with those in the subdural fluid in both CSH and subdural effusion patients (Wilcoxon signed-ranks test). Differences in the values in subdural fluid and in blood between the CSH and subdural effusion patients were analysed (Mann-Whitney-Wilcoxon test). The values in the subdural fluid were also compared between patients with the layering type and the others (Mann-Whitney-Wilcoxon test).

Results

The levels of cytokines in the blood of normal subjects and patients with CSH or subdural effusion are given in Table 1.

The blood from patients with CSH contained levels of TNFα, IL-1β, and IL-6 which were almost within the ranges of normal subjects. The levels of IL-8 in the blood of patients with CSH were slightly higher than those in normal subjects. The subdural fluid from patients with CSH contained the same level of IL-1β and a significantly higher level of TNFα than that in blood (p < 0.05). The levels of IL-6 and IL-8 in the subdural fluid were very much higher than those in blood (p < 0.0001).

The blood from patients with subdural effusion contained TNFα, IL-1β, IL-6, and IL-8, which were almost within the range of normal subjects. The levels of IL-6 and IL-8 were significantly higher in the subdural fluid than those in blood (p < 0.05).

There were no significant differences in levels of cytokines in blood between CSH and subdural effu-

Table 2. IL-8 in the Subdural Fluid of Patients with the Layering Type and Other CSH

<table>
<thead>
<tr>
<th>Type</th>
<th>IL-8 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Layering type</td>
<td>3258.2 ± 1138.3*</td>
</tr>
<tr>
<td>Others</td>
<td>947.9 ± 383.5</td>
</tr>
</tbody>
</table>

* Values are means ± standard errors.

IL-8 interleukin-8.

a p < 0.05 vs. value in others.