Monocyte Chemoattractant Protein-1 Is Increased in the Cerebrospinal Fluid of Patients With Ischemic Stroke

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Background and Purpose—Animal models of stroke have shown that focal cerebral ischemia results in an increased expression of several cytokines and chemokines that precedes leukocyte infiltration into ischemic lesions. The infiltrated leukocytes are thought to contribute to tissue injury in stroke. Monocyte chemoattractant protein-1 (MCP-1) may play an important role in monocyte/macrophage infiltration in stroke patients.

Methods—We studied MCP-1 level in sera and the cerebrospinal fluid of 23 ischemic stroke patients 24 hours after the onset of neurological symptoms and compared the results with 15 control patients with tension headache. The MCP-1 level was determined by ELISA.

Results—There was a significant increase of cerebrospinal fluid MCP-1 level in the studied stroke patients in comparison with the control group. The serum level of MCP-1 did not differ from that of control patients.

Conclusions—Our results suggest that MCP-1 may play a role in the inflammatory reaction during the early phase of ischemic stroke. (Stroke. 2001;32:2695-2696.)

Key Words: chemokines ■ monocyte chemoattractant protein-1 ■ stroke, ischemic

It is well established that cerebral ischemia results in increased expression of several cytokines and chemokines that precedes infiltration of leukocytes into the ischemic lesion.1 These leukocytes contribute to tissue injury in ischemic stroke.2 Monocyte chemoattractant protein-1 (MCP-1) is a potent chemokine specific for monocytes. The expression of MCP-1 mRNA was significantly increased in rat ischemic cortex after either permanent or temporary middle cerebral artery occlusion (MCAO).3 It was also shown that after transient focal ischemia in rats, MCP-1 levels measured in brain tissue increased significantly in the affected hemisphere in comparison with contralateral values.4 These studies performed in animals suggested a significant role of MCP-1 in monocyte/macrophage infiltration into ischemic tissue.

Thus far no studies have been published on MCP-1 levels in human stroke. We decided to detect MCP-1 levels in the cerebrospinal fluid (CSF) and sera of patients with ischemic stroke and to compare results with a control group.

Subjects and Methods

Twenty-three patients of both sexes aged 72.2±10.8 years with first-time ischemic stroke entered the study consecutively. Patients with concurrent diseases or conditions interfering with the aim of the study, such as infections, autoimmune diseases, myocardial infarction, malignancies, any surgical interventions within the previous 12 months, and those on immunosuppressive drugs, were excluded. All patients had completed ischemic stroke, defined as clinical symptoms persisting for >24 hours.5 The diagnosis was based on clinical history and neurological examination and was confirmed by brain CT. The study was approved by the institutional review committee, and all patients gave informed consent, including consent for the lumbar puncture procedure.

Regarding risk factors, 12 patients had hypertension, 4 had diabetes mellitus, 2 had atrial fibrillation, and 5 were smokers. All stroke patients, except 1 with radiologically invisible changes, presented anatomicopathologically relevant CT hypodense areas localized in subcortical parts of the cerebral hemispheres. Twelve strokes were identified as lacunar, 9 as large vessel, and 2 as cardioembolic.

Fifteen individuals with diagnosis of tension headache served as a control group. The control group was matched according to sex and age. No therapy with potential anti-inflammatory properties was given to patients with tension headache before blood and CSF sampling.

CSF and blood samples were obtained 24 hours after the onset of the disease. CSF samples were centrifuged immediately after lumbar puncture and stored at ~80°C. Blood samples were allowed to clot at room temperature for 30 minutes, and after having been centrifuged for 10 minutes, serum was stored at ~80°C. MCP-1 levels in CSF and serum samples were quantified by ELISA (Quantikine R&D Systems) according to the manufacturer’s instructions and measured in duplicate. The sensitivity of the method was 5 pg/mL.

Statistical Analysis

Because the obtained data were not normally distributed, analysis was performed with a nonparametric test. The Mann-Whitney U test was used to compare MCP-1 levels in CSF and serum in stroke patients with control values.

Results

The CSF MCP-1 level in ischemic stroke patients was 857.5±296 pg/mL and was significantly higher (P<0.001)
MCP-1 Levels in CSF and Sera of Patients With Stroke and Control Group

<table>
<thead>
<tr>
<th></th>
<th>Stroke Patients</th>
<th>Control Group</th>
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</thead>
<tbody>
<tr>
<td>CSF</td>
<td>857.5 ± 296*</td>
<td>426.1 ± 143.4</td>
</tr>
<tr>
<td>Serum</td>
<td>287.6 ± 168.8</td>
<td>239.4 ± 141.8</td>
</tr>
</tbody>
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Values are mean ± SD, expressed in picograms per milliliter. *Difference statistically significant (P<0.001).

than that of the control group, in which the level was 426.1 ± 143.4 pg/mL. Serum MCP-1 level was 287.6 ± 168.8 pg/mL in stroke patients and 239.4 ± 141.8 pg/mL in the control group. The difference between these 2 groups was not statistically significant (Table).

Discussion

The present study shows a significant increase of MCP-1 in the CSF of patients with ischemic stroke. Such a result could be expected from previous studies in animals in which increased expression of MCP-1 mRNA in rats was observed, which peaked at 24 to 48 hours after MCAO. In this model of ischemia, neutrophils first infiltrate into the ischemic brain and peak at 24 hours, whereas monocytes/macrophages are recruited later and gradually increase in number after 48 hours from the onset of ischemia. MCP-1 specifically attracts monocytes. The source of this chemokine seems to be endothelial cells and macrophage-like cells. Increased expression of MCP-1 mRNA after MCAO, together with our observation of the significant increase in the level of MCP-1 in the CSF in patients with ischemic stroke, suggests a role of this chemokine in attracting monocytes into the ischemic brain. To confirm this suggestion, the effect of inhibiting MCP-1 on stroke should be evaluated in further studies. It is possible that risk factors present in studied patients may have some influence on inflammation through arterial wall dysfunction or silent parenchymal damage. Thus far there are no studies on risk factors in relation to CSF MCP-1.

MCP-1 may act together with other chemokines, such as macrophage inflammatory protein-1 and cytokine-induced neutrophil chemoattractant; in both of these chemokines, increased mRNA expression was also observed in the ischemic rat brain. The systemic increase of interleukin-8 mRNA expressing mononuclear cells and interleukin-8 levels in plasma from patients with ischemic stroke was found as well, suggesting involvement of interleukin-8 in recruiting blood polymorphonuclear leukocytes to the sites of cerebral ischemia. Chemokines, together with adhesion molecules such as vascular cell adhesion molecule-1, which in soluble form was observed to increase in patients with acute ischemic stroke, appear to be responsible for accumulation of inflammatory cells in ischemic stroke and to contribute with other factors, including several cytokines, to the pathomechanism of human stroke.

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