Intrathecal Expression of Proteins Regulating Apoptosis in Acute Stroke

E. Tarkowski, MD, PhD; L. Rosengren, MD, PhD; C. Blomstrand, MD, PhD; C. Jensen, MD; S. Ekholm, MD, PhD; A. Tarkowski, MD, PhD

Background and Purpose—The neuronal death that accompanies an ischemic stroke has previously been attributed to a necrotic process. However, numerous studies in experimental models of ischemia have recently indicated that programmed cell death, also called apoptosis, may contribute to neuronal death. The aim of the present study was to investigate the intrathecal levels of proteins regulating apoptosis in acute stroke and to relate these levels to brain damage and to production of proinflammatory and anti-inflammatory cytokines.

Methods—Thirty stroke patients were studied prospectively on days 0 to 4, 7 to 9, 21 to 26, and after day 90 with clinical evaluation, radiological assessment, and analysis of cerebrospinal fluid (CSF) levels of soluble (s) Fas/APO-1 and sbcl-2, 2 proteins that regulate apoptosis. In addition, analysis of the intrathecal levels of cytokines interleukin (IL)-1β, IL-6, IL-8, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor-α was performed. Nineteen CSF samples from healthy subjects were used for control purposes. The patients were examined with MRI 1 to 3 months after stroke onset for measurement of infarct volume.

Results—Significantly decreased CSF levels of sFas/APO-1 were observed during the entire observation period, with a maximal decrease on day 21 after the onset of stroke. The intrathecal levels of sFas/APO-1 were significantly negatively correlated with the volume of brain infarct and with the neurological deficit 3 weeks and 3 months after the onset of the stroke. In addition, the intrathecal levels of sFas/APO-1 were significantly correlated with the levels of IL-1β, IL-6, IL-10, and GM-CSF 3 weeks after the onset of the disease. The intrathecal levels of sbcl-2 were significantly decreased during the first 3 days after stroke onset and at the same time were positively correlated with the levels of IL-6 and tumor necrosis factor-α.

Conclusions—Our study demonstrates decreased intrathecal levels of proteins with antiapoptotic properties, suggesting that patients with acute stroke display a propensity toward apoptosis. Control of factors regulating apoptosis may lead to decreased delayed brain damage in stroke. (Stroke. 1999;30:321-327.)

Key Words: apoptosis ■ brain ■ cerebrospinal fluid ■ cytokines ■ magnetic resonance imaging ■ proteins ■ stroke

Stroke is a common disease, leading to a high mortality and disability rate and consequently referred to as “the big crippler.” The clinical outcome of the disease is not only dependent on the extent of the brain lesion but also on its localization. Thus, one of the aims of the research of the last decade has been to delineate the pathophysiological mechanisms that lead to neuronal cell death after compromised blood circulation and energy supply. Neuronal cell death can occur acutely in the core of the infarcted area if the blood flow is <10 mL/100 g tissue per minute and may extend to the penumbral area even after reestablishment of the blood circulation. Several factors, such as acidosis, changes in calcium homeostasis, increased outflow of excitatory amino acids, and free oxygen radical–mediated damage, have been implicated in both acute and delayed cell death. In addition, a growing body of evidence stresses the role of inflammatory mechanisms in the pathophysiology of ischemic brain damage.

The neuronal death that accompanies an ischemic stroke has previously been attributed to necrotic processes in the brain tissue. However, numerous studies in experimental models of ischemia have now reported that apoptosis contributes to neuronal death (reviewed by Chalmers-Redman et al⁷). Apoptosis requires the activation of a “cell death” gene program, and many of the extracellular signals that regulate apoptosis have been identified. For example, interaction between the Fas/APO-1 molecule, a cell surface protein, with its ligand (Fas-L) leads to programmed cell death. Soluble (s) Fas/APO-1, a molecule lacking the transmembrane domain of Fas/APO-1, blocks apoptosis by inhibiting interaction between Fas/APO-1 and Fas-L on the cell surface. Fas expression has been detected on B and T cells and on...
neutrophils. It has been suggested that the Fas/Fas-L pathway is one of the major mechanisms for T-cell–mediated cytotoxicity.8,10,11 Importantly, it has been recently demonstrated by in situ hybridization that the expression of Fas/APO-1 was induced in murine brain after transient global cerebral ischemia.12 In this respect, inhibition of apoptosis after brain ischemia in a rat model of focal ischemia reduces the size of brain infarct.13 Another gene product, bcl-2, has been shown to suppress apoptosis14,15 and to protect primary neuronal cells from apoptosis induced by nerve growth factor depletion.16,17 Overexpression of bcl-2 in transgenic mice protects neurons from naturally occurring death in experimental cerebral ischemia.17,18 Macrophages and T lymphocytes kill target cells by inducing apoptosis, one of the potential mechanisms whereby the inflammatory cells invading the infarcted brain area participate in neuronal cell death.8,10,11 Interestingly, Chopp et al20 have demonstrated in a recent study that antibodies against adhesion molecules not only reduce inflammatory response and volume of infarction in an experimental stroke model but also reduce apoptosis.

We recently demonstrated that stroke patients displayed an intrathecal production of proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF), and of the anti-inflammatory cytokine IL-10 within the first 24 hours after the onset of symptoms, supporting the notion of localized immune response to the acute brain lesion in humans.21,22 Some of these cytokines (eg, IL-1β and IL-8) stimulate influx of leukocytes to the infarcted brain, a prerequisite for Fas/APO-1– and bcl-2–mediated apoptosis. The aim of the present study was to analyze the intrathecal release of sFas/APO-1 and sbcl-2, 2 proteins that suppress apoptosis, and to relate their levels to the size of brain lesions and the intrathecal release of proinflammatory and anti-inflammatory cytokines during stroke.

Subjects and Methods

Patients

Thirty patients (23 men and 7 women; age range, 40 to 81 years; mean ± SD age, 64 ± 11 years), all patients at Sahlgrenska University Hospital, Department of Neurology, were consecutively incorporated into the study. All patients had experienced stroke ≤3 days before inclusion. No patients had a history of previous stroke. Patients with malignant and autoimmune diseases or severe infections or taking immunosuppressive drugs were excluded. All patients were evaluated by a standardized examination of motor and sensory deficit, peripheral reflexes, muscular tone, and cranial nerve function. Occurrence of dysphasia and tactile neglect symptoms was also evaluated. Furthermore, the patients were examined according to the Scandinavian Stroke Scale23 at the inclusion in the study and then 1 week, 3 weeks, and 3 months after onset. The Scandinavian Stroke Scale has a score ranging from 58 (normal neurological status) to 0 (maximal neurological deficit of the scale). The degree of disability was evaluated by the Barthel Index24 3 months after onset (score ranging from 100 = no disability to 0 = complete dependence for activities of daily life). All patients were examined with CT of the brain during the first days after onset of stroke. Twenty patients were reexamined with MRI and the remaining 10 patients with CT 1 month after stroke onset.

Stroke patients were stratified into minor and major stroke groups, according to the classification of Hachinski.25 The definition of minor stroke requires that the patient is discharged and sent home, walks without assistance, and copes unaided with such self-care activity as eating, dressing, and toileting within 1 month after the disease onset.26 In contrast, patients with major stroke had stable and usually severe neurological deficit.

Cerebrospinal fluid (CSF) samples were obtained for analysis of cytokine levels on days 0 to 4, 7 to 9, 21 to 26, and 3 months after disease onset21,22 and for analysis of Fas/APO-1 and bcl-2 (present study). In 10 patients, serum and CSF samples could be obtained twice within the first 4 days after the stroke onset. CSF samples from 19 control individuals without any neurological disease or deficit aged 49 to 78 years (mean ± SEM age, 65 ± 2 years) were obtained to establish the reference values for Fas/APO-1 and bcl-2.

The study was approved by the Ethics Committee of the University of Göteborg.

Reagents and Procedures

Analysis of Soluble Fas/APO-1 and bcl-2

Levels of Fas/APO-1 and of bcl-2 in CSF and serum samples were estimated by a sandwich ELISA (Calbiochem). The detection levels for Fas/APO-1 and bcl-2 were 0.07 U/mL and 1 U/mL, respectively. All values below the detection levels were considered negative.

Cytokine Analysis

Levels of GM-CSF, IL-8, and IL-10 in CSF samples were estimated by an ELISA with the use of monoclonal antibodies for coating and developing steps, as previously described.23 Levels of tumor necrosis factor-α (TNF-α) in CSF samples were estimated by an ELISA (Predicta, Genzyme).

The detection levels for GM-CSF, IL-8, IL-10, and TNF-α were 40, 3, 25, and 2 pg/mL, respectively. The CSF was diluted 10 times for IL-8 and TNF-α determinations and 5 times for GM-CSF and IL-10 measurements. All values below the detection levels were regarded as negative.

Levels of IL-1β in CSF and serum samples were estimated by an ELISA (Quantikine R&D Systems). The normal levels of serum IL-1β are <3.5 pg/mL according to the manufacturer’s data.

IL-6 Assay

Cell line B13.29, which is dependent on IL-6 for growth, has been previously described.27 For IL-6 determinations, the more sensitive subclone B9 was used.28,29 B9 cells were harvested from tissue culture flasks, seeded into microtiter plates (Nunc) at a concentration of 5000 cells per well, and cultured in Iscove’s medium supplemented with 5×10^−3 mol/L 2-mercaptoethanol, 5% fetal calf serum (Seralab), penicillin (100 U/mL), and streptomycin (100 µg/mL), and CSF or serum samples were added. [3H]thymidine was added after 68 hours of culturing, and the cells were harvested 4 hours later. The samples were tested in 2-fold dilutions and compared with a recombinant human IL-6 standard (Genzyme). B9 cells were previously shown not to react with several recombinant cytokines, including IL-1α, IL-1β, IL-2, IL-3, IL-5, GM-CSF, TNF-α, and interferon-γ. There was only weak reactivity with IL-4.29

To assess the specificity of the bioassay, we used a highly purified monoclonal antibody specific for human IL-6 (Genzyme) in a neutralization assay. Preincubation of 10 µg/mL of this antibody with either recombinant IL-6 or CSF from stroke patients containing IL-6 (1 hour, 37°C) reduces proliferative responses of B9 indicator cells by an average ≥95%.

MRI and CT Scan Analyses

To evaluate the final extent and localization of brain lesions, neuroimaging was performed ≥4 weeks after the onset of stroke. This delay in imaging was chosen to obtain a better delineation of the permanent damage. The neuroimaging techniques used were CT as well as multiplanar MRI. The CT scans were routinely performed parallel to the canthomeatal plane, ie, a gantry tilt ≈10° from Reid’s baseline using 5-mm (posterior fossa) and 10-mm (supratentorial) slice thickness. The MRI examinations (Philips Gyroscan T5-II) were performed with conventional fast spin-echo technique to obtain axial proton-density and T2-weighted images of the brain. If a lesion was identified, a 3-dimensional volume sampling was also
performed with the use of a T1-weighted coronal fast gradient-echo technique (repetition time, 30 ms; echo time, 13 ms; flip angle, 30°) with 3-mm slice thickness (scan matrix = 205 × 256 and field of view = 220). All scans were evaluated to correlate each lesion with its anatomic location. The evaluation of the scans was done by 2 experienced neuroradiologists without knowledge of clinical data. Sixty-six important anatomic brain structures were defined in the scans according to Kretschmann and Weinrich,30 and all the lesions were related to these structures. Volume measurements of the lesions were done by means of a 3-dimensional reconstruction program in the workstation environment (Philips Gyroview). This technique entails the use of a proper segmentation and subsequent seeding within the lesion. The imaging sequence used for 3-dimensional sampling resulted in a sharp contrast between these ischemic lesions and the surrounding normal tissue, making lesion segmentation easy. The volume of the lesion thus created is automatically given when reconstruction is finished.

Statistical Analysis
Statistical analysis was performed by the Mann-Whitney U test. The χ² test was used to analyze categorical data. Spearman’s rank order correlation test was used to calculate the correlations between different parameters. A P value < 0.05 was considered statistically significant.

Results
Clinical Findings
Twenty-three patients included in the study displayed varying degrees of hemiparesis when examined at the onset of stroke. Eighteen of the hemiparetic patients were able to perform some voluntary movements, whereas 5 had complete paralysis. Seven displayed no motor deficit but showed other stroke-related symptoms, such as isolated hemisensory deficit or aphasia.

Twelve patients displayed impaired sensory function; 4 of these patients displayed neglect symptoms. Eight had dysarthria. Thirteen patients had neurological signs on the right side of the body, 16 on the left side, and 1 on both sides. Twenty-four patients were classified as having a minor and 6 as having a major stroke.

Use of the Scandinavian Stroke Scale showed that the average neurological deficit was limited during the first days after disease onset (mean ± SD, 47.9 ± 2.3) and diminished in course of time (day 7 to 9, 50.9 ± 2.4; day 21 to 26, 53.8 ± 1.9; after 3 months, 54.2 ± 1.9). The degree of disability, measured 3 months after the onset of stroke by the Barthel Index, was also low (92.6 ± 3.4), indicating that the majority of the patients could perform daily life activities without any help.

Radiological Findings
Thirteen patients exhibited a single infarct, 13 exhibited multiple infarcts, and 4 had no pathological MRI changes in support of infarct. Seventeen patients displayed white matter lesions in the unaffected brain hemisphere, whereas in the remaining 13 patients such changes were not found. Thirteen patients had a large infarct (ie, the sum of the largest transverse and sagittal diameter divided by 2 was > 1.5 cm), and 13 had a small infarct (ie, the sum of the largest transverse and sagittal diameter divided by 2 was < 1.5 cm). The 4 patients with no radiologically visible infarct changes were assumed to have a small infarct. Fourteen patients had an infarct mainly (> 50%) located in the gray matter, and 10 had an infarct mainly located in the white matter. Nine patients had a cortical lesion, and 17 patients had a subcortical lesion.

MRI analysis of brain infarcts in 20 stroke patients revealed that the mean ± SEM lesion volume was 2.2 ± 0.8 mL.

CSF Levels of sFas/APO-1
Only 9 of the 30 stroke patients but 16 of the 19 controls exhibited detectable levels of sFas/APO-1 in the CSF within the first days after disease onset (P < 0.001). The intrathecal levels of sFas/APO-1 were significantly decreased in stroke patients compared with controls during the entire observation period, with a maximal decrease at day 21 after onset (Figure 1).

CSF Levels of sFas/APO-1 in Relation to Radiological Findings
The CSF levels of sFas/APO-1 3 months after stroke onset were significantly negatively correlated (r = -0.47; P < 0.05) with the volume of the brain lesion measured by MRI. No statistically significant correlation was found between the sFas/APO-1 levels in CSF and the brain lesion volume during the first 3 weeks after the onset of the disease (day 0 to 4: r = -0.38, P = NS; day 7: r = -0.13, P = NS; day 21: r = -0.42, P = NS).

Patients with a brain lesion affecting mainly (> 50%) the gray matter did not show any statistically significant differences in CSF sFas/APO-1 levels compared with patients with mainly white matter lesions (Table 1). No statistically significant difference was found between the patients with a single brain lesion and patients with multiple infarcts or between patients with white matter damage in the hemisphere contralateral to the ischemic brain lesion and patients without white matter lesions (data not shown). Patients with cortical lesions and patients with subcortical lesions did not display any statistically significant differences in sFas/APO-1 levels in the CSF (Table 1). Patients with left-sided brain lesions and patients with right-sided brain lesions exhibited similar levels of sFas/APO-1 levels in the CSF (data not shown).
sFas/APO-1 levels in the CSF in Relation to Clinical Findings

Interestingly, there was a significant correlation between the levels of sFas/APO-1 in CSF and the Scandinavian Stroke Scale score 3 weeks after stroke onset ($r=0.42$, $P=0.05$), indicating that stroke patients with low score, ie, pronounced neurological deficit, had low CSF levels of sFas/APO-1. When analyzed separately, patients with a minor and major stroke did not show any statistically significant differences in the sFas/APO-1 levels in CSF (data not shown). No statistically significant correlation between Barthel Index and CSF levels of sFas/APO-1 was found ($r=0.18$, $P=NS$).

**TABLE 2. Correlation ($r$) Between Levels of sFas/APO-1 and Cytokine Levels Measured Concomitantly in CSF of Stroke Patients**

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Day 0–4</th>
<th>Day 7–9</th>
<th>Day 21–26</th>
<th>Day &gt;90</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>0.10</td>
<td>NS</td>
<td>0.69</td>
<td>0.0001</td>
</tr>
<tr>
<td>IL-6</td>
<td>-0.09</td>
<td>NS</td>
<td>0.44</td>
<td>0.042</td>
</tr>
<tr>
<td>IL-8</td>
<td>-0.18</td>
<td>NS</td>
<td>0.29</td>
<td>NS</td>
</tr>
<tr>
<td>IL-10</td>
<td>-0.02</td>
<td>NS</td>
<td>0.46</td>
<td>0.029</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>0.20</td>
<td>NS</td>
<td>0.52</td>
<td>0.012</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.05</td>
<td>NS</td>
<td>-0.48</td>
<td>0.022</td>
</tr>
</tbody>
</table>
significantly decreased in stroke patients compared with the controls during the first 4 days of the disease (Figure 2).

**CSF Levels of bcl-2 in Relation to Radiological Findings**

The bcl-2 levels in CSF were highly significantly correlated with the volume of brain lesion during the first 4 days after the onset of the disease (day 0 to 4, \( r = 0.68, P = 0.003 \)). When analyzed separately, patients with small brain lesions displayed significantly lower levels of bcl-2 in CSF during the first 4 days after stroke onset than the patients with large brain lesions \( (P = 0.006) \) (Table 1) and controls \( (P = 0.0001) \).

Interestingly, patients with subcortical lesions showed initially significantly lower levels of bcl-2 than the patients with cortical lesions \( (P = 0.015) \) (Table 1) and controls \( (P = 0.009) \). In addition, patients with a brain lesion affecting mainly the white matter displayed significantly lower levels of bcl-2 in CSF compared with patients with mainly gray matter lesions \( (P = 0.02) \) (Table 1) and controlled with controls \( (P = 0.006) \) 3 months after stroke onset. In contrast, no statistically significant difference in CSF levels of bcl-2 was found between patients with a single brain lesion and patients with multiple infarcts or between patients with white matter damage in the hemisphere contralateral to the ischemic brain lesion and patients without white matter lesions (data not shown). Patients with right-sided or left-sided brain lesion displayed almost equal levels of CSF bcl-2 (data not shown).

**sbcl-2 Levels in CSF in Relation to Clinical Findings**

Patients with a minor versus major stroke did not show any statistically significant differences in the sbcl-2 levels in CSF (data not shown). No statistically significant correlation between the Scandinavian Stroke Scale or the Barthel Index and CSF levels of sbcl-2 was found (data not shown).

**CSF Levels of bcl-2 in Relation to Intrathecally Produced Cytokines**

A significant correlation was found between the CSF levels of bcl-2 and the CSF levels of the proinflammatory cytokines IL-6 \( (r = 0.43, P = 0.026) \) and TNF-\( \alpha \) \( (r = 0.41, P = 0.036) \) measured during the first days of the stroke. In contrast, GM-CSF levels were negatively correlated with the levels of bcl-2 at 3 weeks \( (r = -0.37, P = 0.002) \) after stroke onset (Table 3).

**Discussion**

Our study has shown a significant decrease of sFas/APO-1 and sbcl-2, 2 proteins that suppress apoptosis, in the CSF of patients with acute stroke. In addition, the CSF levels of sFas/APO-1 were negatively correlated with the degree of neurological deficit and with the volume of brain infarct 3 weeks and 3 months, respectively, after the onset of the disease.

A growing body of evidence points out the role of apoptosis as contributing to the cell death occurring in the

---

**TABLE 3. Correlation \( (r) \) Between Levels of sbcl-2 and Cytokine Levels Measured Concomitantly in CSF of Stroke Patients**

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Day 0–4</th>
<th>Day 7–9</th>
<th>Day 21–26</th>
<th>Day &gt;90</th>
</tr>
</thead>
<tbody>
<tr>
<td>bcl-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>-0.26 NS</td>
<td>0.15 NS</td>
<td>0.09 NS</td>
<td>0.18 NS</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.43 0.026</td>
<td>0.21 NS</td>
<td>-0.23 NS</td>
<td>-0.01 NS</td>
</tr>
<tr>
<td>IL-8</td>
<td>-0.18 NS</td>
<td>0.16 NS</td>
<td>-0.06 NS</td>
<td>-0.21 NS</td>
</tr>
<tr>
<td>IL-10</td>
<td>-0.07 NS</td>
<td>-0.29 NS</td>
<td>0.03 NS</td>
<td>0.01 NS</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>-0.31 NS</td>
<td>-0.25 NS</td>
<td>-0.48 0.031</td>
<td>-0.37 0.002</td>
</tr>
<tr>
<td>TNF-( \alpha )</td>
<td>0.41 0.036</td>
<td>0.49 0.018</td>
<td>0.21 NS</td>
<td>0.51 0.016</td>
</tr>
</tbody>
</table>

---
brain as a consequence of ischemia. For example, the expression of Fas/APO-1 mRNA is induced in some neuronal and glial cells after brain ischemia, suggesting that apoptotic cell death is mediated by the Fas antigen in the postischemic brain. The detection of the Fas-L in the CSF in patients after severe head trauma suggests strongly that the Fas/Fas-L pathway may have a pivotal role in causing local tissue destruction in brain. Several mechanisms may downregulate Fas-mediated cell death. For example, Cheng et al detected a soluble form of Fas/APO-1 protein lacking a transmembrane domain in the CSF of patients with systemic lupus erythematosus. sFas/APO-1 is generated by alternative splicing of Fas mRNA and blocks apoptosis by inhibiting binding between Fas/APO-1 and Fas-L or sFas-L. The Fas-triggered cell death may be partially inhibited by over-expression of bcl-2 and its binding protein BAG-1. Consequently, a decrease of proteins downregulating Fas-mediated apoptosis, seen in our study, together with the increased expression of Fas/APO-1 in the brain tissue after an ischemic lesion, as observed by Matsuyama et al, may result in increased apoptosis, leading to aggravated tissue damage during stroke. Thus, the decreased levels of molecules inhibiting apoptosis observed in our study could be associated with a poorer prognosis. Indeed, the present study demonstrated an inverse correlation between the CSF levels of sFas/APO-1 and the volume of brain infarct on one hand and the degree of neurological deficit on the other, supporting this hypothesis.

An important issue is whether the decreased levels of proteins downregulating apoptosis observed in the present study are due to decreased production, increased consumption, or both. Interestingly, on the day of stroke onset, bcl-2 levels in the CSF were similar to the levels of bcl-2 in controls and then decreased rapidly but transiently. For a number of reasons we believe that increased consumption may be the reason for low intrathecal bcl-2 levels. First, the decrease was observed very rapidly, with kinetics that were more typical for consumption rather than for decreased production. In addition, several experimental studies have shown early-onset apoptosis as a consequence of stroke. In this process, sbcl-2 is consumed because it binds to neurite extension in neurons, thereby counteracting the apoptotic process. Similarly, the levels of Fas/APO-1 are also significantly decreased early (but also late) during the stroke, suggesting receptor-mediated consumption rather than decreased production of this molecule.

Another intriguing issue is the positive correlation between CSF levels of sFas/APO-1 and bcl-2 and locally produced cytokines. A possible explanation for this correlation is the presence of apoptotic cells known to modulate the production of cytokines by immunocompetent cells. In this aspect, Voll et al demonstrated that the presence of apoptotic cells increases the secretion of IL-10 and decreased secretion of TNF-α by monocytes. Cytokines are known to modulate apoptosis. In this respect, Holmin demonstrated that injection of IL-β in rat brain elicited massive DNA fragmentation (ie, apoptosis) within 24 hours, whereas intracerebral injection of TNF-α did not. The IL-1β–mediated apoptosis was primarily confined to neural cells but also to the invading inflammatory cells. Our study points to a highly significant correlation between the intrathecal levels of sFas/APO-1 and IL-1β. In contrast, TNF-α, a powerful cytokine inducing apoptosis in the extraneurial compartment of the body, has been demonstrated to protect rat hippocampal, septal, and cortical cells against metabolic-excitotoxic insults and to facilitate regeneration of injured axons. More importantly, TNF-α and β protect neurons against amyloid β-protein–triggered toxicity. In the present study we observed a significant correlation between the intrathecal bcl-2 levels and the intrathecal TNF-α levels during the first week of the stroke and later, suggesting that this cytokine might have neuroprotective properties by downregulating the process of apoptosis. Indeed, we recently demonstrated that TNF-α triggers in vitro human neuronal cell to produce bcl-2.

In conclusion, our study demonstrates decreased intrathecal levels of proteins with antiapoptotic properties, suggesting a propensity toward apoptosis in patients with acute stroke. In addition, the CSF levels of sFas/APO-1 were negatively correlated with the volume of brain infarct and with the degree of neurological deficit 3 months after the onset of the disease, suggesting that the intracerebral decrease of sFas/APO-1 levels is associated with a poorer prognosis. We conclude that control of factors regulating apoptosis may facilitate future attempts to decrease delayed brain damage in stroke.

References


Intrathecal Expression of Proteins Regulating Apoptosis in Acute Stroke
E. Tarkowski, L. Rosengren, C. Blomstrand, C. Jensen, S. Ekholm and A. Tarkowski

Stroke. 1999;30:321-327
doi: 10.1161/01.STR.30.2.321
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/30/2/321

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/