Brain and Plasma Proteins in Spinal Fluid as Markers for Brain Damage and Severity of Stroke

T. Strand, M.D.,* C. Alling, M.D.,† B. Karlsson, M.D.,‡ I. Karlsson, M.D.,† and B. Winblad, M.D.*

SUMMARY Forty well-defined acute stroke patients were investigated for some cerebro-spinal fluid (CSF) markers of cerebral damage. Myelin-basic protein (MBP), tau-fraction, albumin, IgG and transferrin were analyzed on two early occasions after onset of clinical symptoms. Patients with transitory ischemic attack (TIA) had normal values for MBP both at first and second lumbar puncture. Patients with cerebral infarction and haemorrhage had mean MBP concentrations higher than normal at both lumbar punctures. In cerebral infarction there was a significant increase in MBP from the first to the second lumbar puncture. Patients with intracerebral haemorrhage showed the highest mean MBP values and MBP was markedly elevated already at the first lumbar puncture, suggesting different mechanisms of destruction of nervous tissue in cerebral infarction and bleeding. The amount of MBP was also significantly correlated to the visibility of the cerebral lesion at CT-scan and to the short-term outcome of the patients. The tau-fraction, indicating damage to grey matter, was higher than normal in the majority of patients with cerebral infarction and TIA. The concentration of MBP increases with the extent of brain lesion and a high value indicates a poor short-term prognosis for the patient. This study shows that the brain specific MBP in CSF is a useful marker of cerebral damage in acute cerebrovascular disease.

Stroke Vol 15, No 1, 1984

References

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Received December 10, 1981; second revision accepted June 28, 1983.
proteins in CSF and that estimation of such proteins is useful as a measure of damage to nervous tissue proper. Damage to the blood-brain barrier on the other hand can be demonstrated by measuring increased concentrations of blood plasma proteins in CSF.

The tau-fraction demonstrated by electrophoresis of the CSF proteins has been used as a semiquantitative measure for degenerative brain disorders. A quantitative determination of the tau-fraction has been used in this study and is based on the immunological identity of the tau-fraction and transferrin. The lower electrophoretic mobility of the tau-fraction compared to transferrin is due to a loss of sialic acid caused by sialidases, enzymes which are highly concentrated in the synapses and very little of these enzymes is found in the white matter. An increase in the tau-fraction therefore indicates degenerative changes in the cerebral cortex or in brain nuclei.

Myelin-basic protein (MBP) is exclusively located in myelin and an increased concentration of this protein in CSF has been demonstrated in active demyelinating disease, after brain surgery, and also in acute-CVD patients.

The purpose of the present study was to measure the CSF concentrations of MBP, tau-fraction, albumin, IgG and transferrin in a well-defined clinical sample of acute-CVD patients, to demonstrate the significance of the substances as markers of acute CVD, and to correlate these markers to the type and size of brain lesion and to the patient’s clinical outcome.

Materials and Methods

Patients

Forty patients (23 men, 17 women, mean age 71.0 years) admitted consecutively to the Stroke Unit, Dept. of Medicine, University Hospital of Umeå, were studied. The Stroke Unit is a special six-bed care and research unit for patients with acute well-defined CVD (focal neurological dysfunction with a duration not exceeding one week). The mean delay between the onset of symptoms and admission to hospital was 18 hours (range 2–56 hours). Patients with only dizziness and/or disturbances of consciousness without focal neurological signs are not admitted. Every patient is investigated in a standardized manner including computed tomography of the brain (EMI Mark 1, Head Scanner), if possible on two occasions after symptom onset (mean day 1 and day 8), and lumbar punctures with spinal fluid spectrophotometry (mean day 1 and day 5, range day 0–3 and day 4–8). The clinical assessment of the patients is performed by a specially-trained physician from the stroke team on day 0, day 1, day 4 and on discharge. Regimens for treatment are uniform and the unit has resources for early active mobilization and rehabilitation. The patients stay at the unit until they are able to go home or are transferred to a longstay ward.

Cerebral infarction

A focal neurological deficit of more than 24 hours duration with a CT scan exhibiting a low attenuating (hypodense) area or a normal picture. If the CT scan was normal or hard to evaluate because of movement artifacts and spinal fluid spectrophotometry showed a bleeding pattern, the diagnoses varied from intracerebral haemorrhage (clear obvious bleeding pattern without contamination of blood at the puncture site and normal CT scan) to infarction with bleeding and unspecified cerebrovascular diagnosis.

Cerebral haemorrhage

A high attenuating area (hyperdense) in the CT scan and/or a clear haematoma pattern in spinal fluid spectrophotometry.

TIA

A focal neurological deficit with total regression within 24 hours.

RIND

A reversible ischaemic neurological deficit. Total or almost total regression of the neurological deficit after more than 24 hours. These patients were diagnosed as examples of cerebral infarction or haemorrhage, according to above-listed criteria.

Prognosis

The observation time is the time the patients stay at the Stroke Unit. The patients who need prolonged care remain between 1–2 months at the unit before transfer to a longstay hospital. All deaths included in this study occurred during the time spent at the Stroke Unit.

Spinal-fluid sampling

Approximately 12 ml of spinal fluid were obtained from the patients, lying in a horizontal position, on two occasions, mean day 1 (range 0–3) and day 5 (range 4–8). In two patients, only one lumbar puncture could be performed. Samples of 4–6 ml of CSF were used for the purpose of this study. The fluid was kept at −80°C until analysis. The concentrations of albumin, transferrin, IgG, MBP and tau-fraction were determined after fluid had been collected from all of the patients.

Myelin basic protein

Isolation and purification of myelin-basic protein was performed according to Deibler et al and production of antiserum as described previously. The assay of myelin-basic protein was performed with a radiimunological method as described by Karlsson and Alling using cold ethanol in the precipitation step. Increased levels of plasma proteins, including IgG in CSF, has not been found to correlate with increasing levels of myelin-basic protein. The measurements were made on 400 µl spinal fluid in a total volume of 560 µl. The detection limit was 1.25 µg/l spinal fluid. Based on clinical information and the existence of normal values in spinal fluid for total protein, albumin, transferrin and IgG, 37 patients selected from routine
analyses in this laboratory were used as normal controls. The concentration of myelin-basic protein in the control group was 2.36 ± 0.81 μg/l (mean ± S.D.). The within-run coefficient of variance was 5.7% and between-run was 8.8%.

Tau-fraction
The tau-fraction was determined using a crossed immunoelectrophoretic method. 10 μl CSF were separated in 0.7% agarose 12 V/cm for 70 min. The second direction was run in 0.7% agarose with antitransferrin (15 μl/10 ml gel, Dakopatt, Denmark) 10 V/cm for 5 h. The transferrin and tau-fractions showed a continuous line of precipitation, and intermediate fractions could only be seen in trace amounts in some of the samples.

The curves presenting the tau fraction and transferrin respectively were cut from photographic reproductions and weighed. The concentration of the tau-fraction was calculated from its proportion of the transferrin concentration, determined by electroimmunoassay. The tau-fraction concentration was determined in 11 psychiatric patients without suspicion of a degenerative brain disease. The mean value was 1.68 ± 0.65 mg/l (mean ± S.D.) suggesting a normal upper limit of 3.0 mg/l (mean ± 2 SD). Within run imprecision was 6.0%.

Albumin, IgG and transferrin
Albumin, IgG and transferrin were determined by electroimmunoassay, according to Laurell. Anti-human albumin, anti-human IgG (heavy chains) and anti-human transferrin anti-serum from rabbits were obtained from Dakopatt A/S, Hellerum, Denmark. Standard human serum (Behringwerke, F.R.G.) was used as standard in the electroimmunoassays. Reference values (n = 50, > 45 years) for the three methods are as follows: albumin 100–400 mg/l, IgG 10–42 mg/l, transferrin 8–30 mg/l. Imprecisions for the three methods are given in detail in a previous paper.

Statistical methods
In comparing two groups with unknown variance with respect to the mean the usual statistical method Student’s t-test has been applied. Firstly, we have used the t-test for paired samples to compare the change in concentration between the first and second puncture of e.g. MBP; secondly, the ordinary t-test was used with pooled or separate variance estimate depending on the F-test of the variance in the compared groups to compare those with visible and non-visible lesions and in comparing patient groups with controls.

Because the t-test is inadequate when comparing three or more groups, Analysis of Variance (ANOVA) has been used to determine if the differences between patients with different diagnoses, on the one hand, and with different extents of brain damage on the other are due to random or real events. In table 4 we have used Spearman’s rank correlation coefficient to compute the linear relationship between MBP and short-term prognosis.

Results
Protein concentrations in the different diagnostic groups

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>MBP (μg/l)</th>
<th>Tau (mg/l)</th>
<th>Albumin (mg/l)</th>
<th>Transferrin (mg/l)</th>
<th>Ig G (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>I</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>2.36</td>
<td>1.68</td>
<td>250</td>
<td>19</td>
<td>27</td>
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<tr>
<td>S.D.</td>
<td>0.81</td>
<td>0.65</td>
<td>75</td>
<td>5</td>
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<tr>
<td>TIA (n = 8)</td>
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</tr>
<tr>
<td>Mean</td>
<td>2.6</td>
<td>2.7</td>
<td>3.9†</td>
<td>4.8†</td>
<td>377</td>
</tr>
<tr>
<td>S.D.</td>
<td>1.2</td>
<td>1.3</td>
<td>1.5</td>
<td>2.3</td>
<td>261</td>
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<tr>
<td>Infarction (n = 23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.8†</td>
<td>10.4†</td>
<td>4.5‡</td>
<td>5.2‡</td>
<td>295</td>
</tr>
<tr>
<td>S.D.</td>
<td>4.0</td>
<td>11.8</td>
<td>2.3</td>
<td>2.6</td>
<td>161</td>
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<td>Haemorrhage (n = 7)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>25.0†</td>
<td>30.1†</td>
<td>2.5</td>
<td>3.2*</td>
<td>680</td>
</tr>
<tr>
<td>S.D.</td>
<td>15.5</td>
<td>19.6</td>
<td>1.1</td>
<td>1.6</td>
<td>571</td>
</tr>
</tbody>
</table>

*p < 0.05; †p < 0.01; ‡p < 0.001 compared with controls

Table 1: Protein Concentrations in Spinal Fluid from Patients with Stroke Obtained on Day 1 (I) and Day 5 (II)
are given in figure 1. This group differed from controls both at first and second lumbar puncture (p < 0.01). Ten patients had increased values in the first puncture (compared to controls) and seven of them were further increased in the second puncture. Seven patients had normal values on the first occasion and increased to concentrations above 4 μg/l on the second occasion. In three patients with an increased value in the first puncture, a slight decrease took place. The mean concentration of the tau-fraction was 15% higher in the second puncture compared to the first puncture (p < 0.01; Student's t-test, paired samples). The tau-fraction was increased in both first and second puncture (p < 0.001). In 14 of these patients, the tau-fraction was increased on both occasions. The mean value of albumin was normal but the concentrations of IgG and transferrin were higher than normal in both punctures (p < 0.01).

Haemorrhage (table 1)

In the first and second puncture, the concentrations of MBP were considerably above normal (p < 0.001) (fig. 1). Two patients, however, had normal values in the first puncture. In one of these cases the clinical diagnosis was uncertain, with normal CT-scan pictures on both occasions, and the diagnosis was based on clinical and spectrophotometric findings. The other patient was difficult to classify because she developed a large haemorrhage in an infarcted area during heparin treatment. In her second lumbar puncture, the MBP value was high. In two patients with haemorrhage, only one puncture was performed. Their values of MBP were 12.9 μg/l (day 4) and 51.0 μg/l (day 1). The mean value for the tau-fraction in all patients was normal in the first puncture and slightly higher in the second. The IgG and transferrin concentrations were increased on both occasions (p < 0.05).

Protein concentrations in relation to extent of brain damage

In table 2 it may be seen that the mean concentration of MBP was significantly increased in both first (p = 0.005; Student's t-test) and second (p < 0.001) lumbar punctures in patients with visible lesions on CT scan when compared to those CVD patients without visible lesions. This is also illustrated in the cumulative curves in figure 2 from which it is easy to compute the median. The concentrations were highest in patients with the largest infarctions and greatest haemorrhages. No such difference was observed for albumin, IgG or transferrin. On the contrary, the mean concentration of the tau-fraction in both punctures was somewhat higher in patients with no visible lesions.

In table 3 it may be seen that an increasing degree of disability was related to an increasing mean concentration of MBP in both lumbar punctures (p < 0.001; one-way analysis of variance, ANOVA). Patients with TIA and RIND had the lowest mean MBP concentrations. In the most severely neurologically-handicapped group, the mean values for MBP were more than five times higher than in the TIA and RIND groups. The ranges were wide in all groups. For the tau-fraction, albumin and transferrin, no relationship was found similar to that found for MBP. For IgG, however, there was, in the second lumbar puncture, a significant difference between the means in the three disability groups for IgG (p = 0.001, ANOVA).

Table 4 shows the prognosis for neurological deficit and mortality for patients with certain values of MBP.

---

**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>Visible lesion</th>
<th>Non visible lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MBP I</td>
<td>MBP II</td>
</tr>
<tr>
<td>Mean</td>
<td>17.4*</td>
<td>23.6†</td>
</tr>
<tr>
<td>S.D.</td>
<td>16.2</td>
<td>16.4†</td>
</tr>
<tr>
<td>Tau I</td>
<td>3.6</td>
<td>3.7</td>
</tr>
<tr>
<td>S.D.</td>
<td>2.1</td>
<td>1.9</td>
</tr>
<tr>
<td>n</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

Lesions were defined as low or high attenuating areas in the brain tissue. Patients with only dilatation of the ventricles were classified in the group "no visible lesion." Patients in whom CT-scan were not performed or which were impossible to evaluate due to movement artifacts were excluded.

* p < 0.01; † p < 0.001
TABLE 3 Concentration of MBP and of the Tau Fraction in First and Second Lumbar Puncture in Patients with Graded Severity of Symptoms

<table>
<thead>
<tr>
<th></th>
<th>MBP I</th>
<th>MBP II</th>
<th></th>
<th>MBP I</th>
<th>MBP II</th>
<th></th>
<th>MBP I</th>
<th>MBP II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>0.0–10.5</td>
<td>0.0–11.3</td>
<td>1.8–19.5</td>
<td>0.3–23.8</td>
<td>2.3–51.0</td>
<td>5.8–48.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>3.5</td>
<td>3.7</td>
<td>5.2</td>
<td>6.8</td>
<td>18.8</td>
<td>28.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.D.</td>
<td>2.3</td>
<td>2.6</td>
<td>4.8</td>
<td>6.5</td>
<td>17.3</td>
<td>16.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tau I</td>
<td>Tau II</td>
<td></td>
<td>Tau I</td>
<td>Tau II</td>
<td></td>
<td>Tau I</td>
<td>Tau II</td>
</tr>
<tr>
<td>Range</td>
<td>2.0–6.2</td>
<td>1.3–10.1</td>
<td>1.9–10.3</td>
<td>0.8–13.0</td>
<td>1.3–10.2</td>
<td>1.8–7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>3.9</td>
<td>5.2</td>
<td>4.4</td>
<td>5.1</td>
<td>3.7</td>
<td>3.6</td>
<td></td>
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</tr>
<tr>
<td>S.D.</td>
<td>1.5</td>
<td>2.2</td>
<td>2.2</td>
<td>2.8</td>
<td>2.3</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>14</td>
<td>13</td>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

I: Patients with TIA or RIND (reversible ischaemic neurological deficits within 24 hours or more). II: Patients with permanent neurological deficits of lesser degree (can manage all or most of their primary ADL) and III: Patients with high degree of neurological deficits (unable to make their primary ADL and went to long-stay ward or died during hospital stay due to their stroke or to complications).

FIGURE 2. Cumulative distributions and median values (in brackets), of MBP, Tau-fraction, IgG, and Albumin in second lumbar puncture in relation to visibility of brain lesion on CT scan.

Patients with a maximal MBP < 5 µg/l in both lumbar punctures had totally reversible symptoms in 58% (11 patients); 42% (8 patients) had low-degree permanent disability. In patients with maximal MBP > 20 µg/l (11 patients), only 1 patient showed a low degree of disability while 5 patients showed a high degree of disability and needed care in a long-stay ward. All deaths (5 patients) occurred in this group. There was a linear relationship between the MBP values and the short-term prognoses (p < 0.01).

For the tau-fraction, albumin, IgG and transferrin, there is no clear pattern for prognoses at certain values. However, there seemed to be more patients with reversible symptoms and a lesser degree of neurological deficit in the groups with the highest maximal tau value.
The visible lesion and the extent of the lesion at CT scan in cerebral infarction and haematomas is, in most cases, correlated to neurological deficits and prognosis. In cerebral haematomata, the haemorrhage is immediately visible as a hyperdense area and is easy to quantify. In cerebral infarction, the lesion is seen as a hypodense area. This hypodense area is often but not always detectable in the early phase of the ischemic stroke, but in most cases it becomes visible after one week. The concentration of MBP correlated with the existence and extent of brain lesions. The mean concentration of MBP was significantly higher in patients with visible lesions on CT scan compared to those without. The MBP concentrations were higher in patients with large lesions than in those with small. Some patients with normal CT scans had high values of MBP. An explanation for this could be that some infarctions were not visible during the early phase of a stroke, especially those in the posterior fossa; the insensitivity of the scanner could also be a factor.

The clinical outcome and the prognosis in stroke are dependent not only on the extent and localization of the brain lesion but also on such factors as the state of the patient before the stroke and on secondary complications, provided that the treatment is uniform. Therefore, in spite of the small number of patients, it was surprising to find such a good correlation between short-term prognoses and the concentrations of MBP (Table 4). This correlation is obviously explained by the fact that the concentration of MBP in CSF provides information about the amount of white matter that has been damaged, which is in turn, critical for prognosis.

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### Prognosis in Relation to Concentrations of MBP

<table>
<thead>
<tr>
<th>TIA-RIND</th>
<th>Disability of lesser degree</th>
<th>Disability of higher degree</th>
<th>Death</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5.0</td>
<td>11</td>
<td>8</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>5.0–9.9</td>
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<td>3</td>
<td>2</td>
<td>6</td>
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<tr>
<td>10.0–19.9</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>&gt;20.0</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>11</td>
</tr>
</tbody>
</table>

The highest value found in either of the two punctures was selected for grouping the patients. The number of patients is indicated in different disability groups.

Discussion

A conclusive biochemical marker of cerebral damage and prognosis which would be useful for clinical purposes in acute CVD has not yet been found either in CSF or in blood plasma. In this study of a well defined population of acute stroke patients, both MBP and the tau-fraction provided diagnostic information. The mean MBP in CSF was significantly increased in patients with acute cerebral infarction and haemorrhages, indicating destruction of white matter. In a recent study by Whitaker et al, a similar increase in MBP in CSF was found in 13 of 53 patients with stroke, and the degree of elevation seemed to parallel the predicted volume of the lesion but did not correlate to the time delay from the onset. On the other hand, Cohen et al reported that only a minimal number of neurological patients had elevated MBP values, unless the diagnosis was active multiple sclerosis. Unfortunately, he did not state how many of his patients had various types of stroke or whether they were in acute phase or not.

In our study, the increase of MBP in cerebral infarction was most evident about four to five days after the onset. In cerebral haemorrhage, on the other hand, the increase was highest almost immediately after the onset. It seems that the mechanism of destruction due to ischemia is a slower process, suggesting metabolic derangements; while in haemorrhage, a more rapid process takes place, due to the discharge of blood into the tissue. Similar results have been found concerning astrogliosis, another brain-specific protein. That not all patients in our study showed higher MBP values in the second lumbar puncture could be explained by different individual kinetics involved in the release and the elimination of MBP from the spinal fluid and by the localization of the brain lesion. Different time intervals between the onset of symptoms and lumbar puncture must also be considered together with the different dynamics of the brain damage in question. This study of 40 patients does not, however, allow a more detailed analysis of these circumstances. The mean value for the tau-fraction was increased not only in the infarction group but also in the TIA group, indicating an ischemic disturbance of grey matter. Increases in the concentration of the tau-fraction were not correlated to neurological deficit.

#### Table 4 Prognosis in Relation to Concentrations of MBP

<table>
<thead>
<tr>
<th>TIA-RIND</th>
<th>Disability of lesser degree</th>
<th>Disability of higher degree</th>
<th>Death</th>
<th>n</th>
</tr>
</thead>
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<td>6</td>
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<tr>
<td>10.0–19.9</td>
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<td>2</td>
<td>1</td>
<td>4</td>
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<tr>
<td>&gt;20.0</td>
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<td>5</td>
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</table>

The highest value found in either of the two punctures was selected for grouping the patients. The number of patients is indicated in different disability groups.
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Stroke. 1984;15:138-144
doi: 10.1161/01.STR.15.1.138

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