Correlation between Neopterin, Biopterin and Nitrite/Nitrate in Cerebrospinal Fluid in Child Patients with Neurological Diseases

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Abstract

Cerebrospinal fluid (CSF) neopterin been previously reported in various diseases. In this study CSF neopterin, biopterin, and nitrite/nitrate (NOx) contents were measured and the correlation between them in child patients with various kinds of neurological diseases were investigated. Changes in the CSF neopterin levels in patients with bacterial meningitis were similar to those previously reported for those with bacterial meningitis; on the 2nd hospital day they were significantly higher than on admission, and on the 6th hospital day they were tapered. The CSF biopterin levels and CSF NOx content in patients with bacterial meningitis on admission were significantly higher than those with other categories and were decreased gradually. Although patients with high levels of CSF neopterin tended to have high CSF biopterin levels in any categories, there was no significant correlation between CSF neopterin and biopterin levels. The CSF biopterin and NOx levels in patients with convulsions were higher than those with aseptic meningitis. Since the neuro-protective or anticonvulsant role for NO was previously reported, high CSF biopterin and NOx levels in patients having epilepsy or febrile convulsions may be regarded as one of the endogenous mechanisms for recovery from an overexcitatory brain in patients with convulsive diseases.

Key words: cerebrospinal fluid (CSF), neopterin, biopterin, nitrite/nitrate (NOx), meningitis, convulsions

Introduction

Neopterin was reported to be a marker for activation of various kinds of diseases. We previously reported that cerebrospinal fluid (CSF) neopterin levels were much higher in patients with bacterial meningitis than in those with other categories (aseptic meningitis or nonpleocytotic CSF) (1) and that in non-pleocytotic CSF, CSF neopterin levels were higher than in patients with febrile convulsions (FCs) than in those with pyrexia without convulsions or convulsions without pyrexia (2).

On the other hand, a few studies have referred to CSF biopterin (3, 4) or nitrite/nitrate (5) levels.

In the present study, we measured both CSF neopterin and biopterin levels, and CSF nitrite/nitrate (NOx) levels in child patients with various kinds of neurological diseases. We investigated the correlation between them.

Patients and Methods

Forty-one patients (23 males and 18 females) were studied. CSF was collected from patients attending hospitals relating to Nippon Medical School (Second Hospital, Tama Nagayama Hospital, and Hakujuji General Hospital) between June 2000 and Jan., 2002 for a spinal tap under clinical indications. Nine patients (6 males and 3 females) had bacterial meningitis. Hemophilus influenzae was detected in 6 cases, Streptococcus pneumonia in 1 case, Escherichia coli in 1 case, and 1 was undetectable.

Eleven patients (5 males and 6 females) had aseptic meningitis. Significant elevation of viral antibodies in...
sera or CSF was seen in 4 cases (mumps in 2 cases, herpes simplex in 2 cases, respectively). Ten patients (5 males and 5 females) had convulsive diseases. Seven had febrile convulsions, 2 epilepsy (status epilepticus), and 1 seizure accompanying rotavirus infection. Eleven patients (7 males and 4 females) having pyrexia and/or headache but not convulsions were regarded as controls.

Samples were collected three times (on admission, the 2nd hospital day, and the 6th hospital day) in patients with bacterial meningitis because of the need to check the response to medical treatment and the patients' conditions. However, in other categories samples were collected at admission alone. Informed consent was obtained prior to each examination. Samples were kept frozen at -70°C until they were measured. The neopterin and biopterin levels were determined as previously reported (6), using high-performance liquid chromatography with an excitation wavelength set at 350 nm and emission wavelength of 450 nm. The concentrations of NOx were also determined as previously reported (7), using a Griess reagent, which consisted of 1% sulfanilamide, 0.1% naphthyl-ethylenediamine dihydrochloride, and 5% H3PO4. The absorbance at 540 nm was measured. Values were reported as means ± standard deviations and analyzed using the posthoc test (Tukey-Kramer), with values at P<0.05 considered to be statistically significant.

Results

CSF neopterin and biopterin levels in patients with each category

As summarized in the Table 1, in this study, the CSF neopterin levels in patients with bacterial meningitis on admission (42.6±9.4 ng/ml) were similar to those with aseptic meningitis (39.2±4.9 ng/ml) or convulsions (34.3±15.0 ng/ml), and they were significantly higher than those with controls (14.8±5.9 ng/ml). The CSF neopterin levels in patients with bacterial meningitis on the 2nd hospital day (73.3±17.2 ng/ml) were significantly higher than those with bacterial meningitis on admission, aseptic meningitis or convulsions. The CSF neopterin levels in patients with bacterial meningitis on the 6th hospital day (16.1±6.0 ng/ml) were decreased from those at the two previous measuring points.

The CSF biopterin levels in patients with bacterial meningitis on admission (77.4±26.8 ng/ml) were significantly higher than other categories (aseptic meningitis: 23.6±11.2 ng/ml, convulsions: 31.4±15.5 ng/ml, controls: 17.6±6.2 ng/ml). The CSF biopterin levels in patients with bacterial meningitis were decreased gradually (on the 2nd hospital day: 39.1±13.4 ng/ml, on the 6th hospital day: 13.4±4.1 ng/ml). There was a tendency for the CSF biopterin levels in patients with convulsions to be higher than those with aseptic meningitis, but with no significant difference.

The N/B (neopterin/biopterin) ratio in patients with bacterial meningitis on the 2nd hospital day tended to be higher than that on admission, but there was no significant difference between any two categories similar to the N/B ratio.

Table I CSF Neopterin, biopterin, and NO2/NO3 levels in each category

<table>
<thead>
<tr>
<th>Category</th>
<th>Neopterin [ng/ml]</th>
<th>Biopterin [ng/ml]</th>
<th>N/B ratio</th>
<th>NO2/NO3 [μ M/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial meningitis (n=9)</td>
<td></td>
<td></td>
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<tr>
<td>Admission Day</td>
<td>42.6 ± 9.4</td>
<td>77.4 ± 26.8</td>
<td>0.59 ± 0.17</td>
<td>9.17 ± 1.33</td>
</tr>
<tr>
<td>The 2nd hospital day</td>
<td>73.3 ± 17.2</td>
<td>39.1 ± 13.4</td>
<td>2.11 ± 0.85</td>
<td>3.14 ± 0.97</td>
</tr>
<tr>
<td>The 6th hospital day</td>
<td>16.1 ± 6.0</td>
<td>13.4 ± 4.1</td>
<td>1.25 ± 0.44</td>
<td>0.86 ± 0.45</td>
</tr>
<tr>
<td>Aseptic meningitis  (n=11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsions         (n=10)</td>
<td>39.2 ± 4.9</td>
<td>23.6 ± 11.2</td>
<td>2.06 ± 1.07</td>
<td>1.94 ± 0.53</td>
</tr>
<tr>
<td>Controls            (n=11)</td>
<td>34.3 ± 15.0</td>
<td>31.4 ± 15.5</td>
<td>1.11 ± 0.30</td>
<td>5.44 ± 0.95</td>
</tr>
</tbody>
</table>

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was significantly higher than that with other categories (aseptic meningitis: 1.9±0.53 μmol/L, convulsions: 5.4±0.95 μmol/L, controls: 1.52±0.43 μmol/L). The NOx content in patients with bacterial meningitis were decreased gradually (on the 2nd hospital day: 3.14±0.97 μmol/L, on the 6th hospital day: 0.86±0.45 μmol/L). In addition, the NOx content in patients with convulsions was significantly higher than that with aseptic meningitis or controls.

Discussion

We previously reported on CSF neopterin in various diseases (1, 2). In this study, the CSF neopterin levels in patients with bacterial meningitis on the 2nd hospital day were significantly higher than those with bacterial meningitis on admission, those with aseptic meningitis or those with convulsions. The CSF neopterin levels in patients with bacterial meningitis on the 6th hospital day were lower than those with bacterial meningitis on admission. The time course of the CSF neopterin levels in patients with bacterial meningitis similar to the present study was reported as previously (1).

As for CSF biopterin levels in patients with bacterial meningitis on admission, they were significantly higher than any other category (those with aseptic meningitis, convulsions or controls). This actually appeared to be compatible with the central nervous system (CNS) compartment in patients with bacterial meningitis who had greater immunological or biochemical stress than any other categories. In addition, patients with high levels of CSF neopterin tended to have high CSF biopterin levels in any categories. However, there was no significant correlation between CSF neopterin levels and CSF biopterin levels (R=0.31 data not shown). Moreover, although the higher CSF neopterin levels on the 2nd hospital day resulted in a longer period of positive serum C-reactive protein (CRP) (1), there was no correlation found between CSF biopterin levels and serum CRP in this study (data not shown). So, the present findings should support those of the previous study that reported CSF neopterin appears to be a more valuable marker for evaluating the activity of inflammation in the CNS compartment (3).

It was been actually reported that NOx content was significantly increased in patients with bacterial meningitis (4, 5). However, the CSF biopterin and NOX content in patients with convulsions were higher than those with aseptic meningitis. Since the CSF neopterin levels in patients with aseptic meningitis were higher than those with convulsions, it was clear that the immune response in the CNS compartment was stronger in the former than in the latter. Moreover, it was actually reported that some immune activation in the CNS compartment may hypothesize one of the mechanisms of onset of febrile convulsions (2).

However, since a neuro-protective (8) or antiinflamatory (9, 10, 11, 12) role for NO has been reported, high CSF biopterin and NOx levels in patients with convulsions may be regarded as one of the endogenous mechanisms for recovery from an overexcitatory brain in patients with convulsive diseases (epilepsy or febrile convulsions).

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References

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