学 位 論 文 の 要 旨

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学　位　論　文　名　Elevated BAFF Levels in the Cerebrospinal Fluid of Patients With Neuro-Behçet's Disease: BAFF is Correlated With Progressive Dementia and Psychosis

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論 文 内 容 の 要 旨

INTRODUCTION

Neuro-Behçet's disease (NBD) is one of the most serious complications of Behçet's disease and shows a variety of manifestations, the most serious symptom is slowly progressive dementia or psychosis, which is resistant to immunosuppressive treatments and can result in severe deterioration of the patients' personality. However, few immunological markers are known to be associated with the activity or pathogenesis of NBD.

B cell activating factor belonging to the tumor necrosis factor family (BAFF) plays a role in the maturation, proliferation and survival of B cells and in T cell costimulation. Accumulating evidence suggests that BAFF plays an important role in the pathogenesis of immune diseases. Recent reports showed that BAFF is also constitutively expressed at the transcriptional level in normal human brain. In some diseases, such as multiple sclerosis (MS), BAFF protein is expressed by astrocytes in the brain parenchyma and in the perivascular area, and locally increased production of BAFF may contribute to B cell focal survival. In the present study, we investigated a role of BAFF in patients with NBD, and compared it with IL-6 that was previously reported to be associated with slowly progressive NBD.

MATERIALS AND METHODS

Cerebrospinal fluid (CSF) samples were collected from 18 patients with NBD, 27 patients with epidemic aseptic meningitis (AM), 24 patients with MS and 34 healthy subjects.

The CSF samples from patients were collected at diagnosis and those from healthy subjects were collected at orthopedic surgery, after they gave their written informed consent for sample collection in accordance with institutional policy. Serum samples were also obtained from 9 of the 18 NBD patients before the initiation of immunosuppressive therapy. Sera from 24 healthy individuals served as controls, although these individuals were not the same as those used for CSF controls. The concentrations of BAFF and IL-6 in the samples were measured by ELISA. The Kruskal-Wallis test was used to compare BAFF and IL-6 concentrations in CSF from the four groups. The criteria for the post-hoc test were adjusted using the Bonferroni correction. Pearson's correlation coefficient was used to ascertain whether correlations existed between any two parameters. Depending on the response to therapy and their clinical course we subdivided NBD patients into two groups, those with an acute (n=10) and with chronic disease course (n=8), and analyzed the CSF levels of BAFF and IL-6 between those two groups.

RESULTS AND DISCUSSION

In the comparison of BAFF levels in the CSF between the four groups (patients with NBD, AM, MS and healthy subjects), the Kruskal-Wallis test showed a significant effect between the groups ($P < 0.01$), and the post-hoc test showed that BAFF levels in the CSF of NBD patients (6.4 ± 5.1 ng/ml, median; 6.2 ng/ml) were significantly higher than the healthy subjects (1.4 ± 1.2 ng/ml, median; 1.2 ng/ml), ($P = 0.002$). There were no statistically significant differences in the CSF BAFF levels between NBD patients and the other disease controls, including AM (2.2 ± 1.4 ng/ml, median; 1.9 ng/ml) and MS (2.7 ± 2.6 ng/ml, median; 2.4 ng/ml).

Comparison of the CSF IL-6 concentrations in the four groups, showed the mean CSF IL-6 level in NBD patients was 23.0 ± 59.0 pg/ml (median; 1.1 pg/ml), which was higher than that of healthy subjects with a borderline significance ($P = 0.008$). As well as NBD, the post-hoc test indicated significant differences between patients with AM (41.3 ± 88.9 pg/ml, median; 2.4 pg/ml) and healthy subjects (1.1 ± 1.3 pg/ml, median; 0.7 pg/ml), ($P < 0.001$) and between patients with MS (20.5 ± 73.6 pg/ml, median; 2.2 pg/ml) and controls ($P < 0.001$).

There was no difference between serum BAFF levels in patients with NBD at diagnosis (7.9 ± 7.6 ng/ml, median; 5.5 ng/ml) and those in healthy subjects (10.5 ± 4.8 ng/ml, median; 10.2 ng/ml). There was also no difference between serum IL-6 levels in patients with NBD (41.8 ± 59.5 pg/ml, median; 15.2 pg/ml) and healthy subjects (36.7 ± 63.9 pg/ml, median; 15.8 pg/ml).

We examined the association of CSF BAFF levels with serum BAFF level and CSF cell parameters in NBD, no significant correlation was detected between CSF and serum BAFF levels in NBD patients whose sera were available (n = 9, r = 0.45, $P = 0.22$). CSF BAFF levels did not correlate with CSF cell counts (r = -0.29, $P = 0.34$). Furthermore, no association was

found between CSF BAFF and CSF IL-6 levels in NBD (r = 0.06, P = 0.82). In contrast, IL-6 levels significantly correlated to CSF cell counts (r = 0.59, P = 0.009).

Next, patients with NBD were subdivided into two groups depending on their response to therapy; 10 patients with an acute course who responded to immunosuppressive therapy and 8 patients with a chronic course who presented psychosis and dementia. CSF BAFF levels at diagnosis were significantly higher in patients with a chronic course (n = 8, 10.2 ± 4.0 ng/ml, median; 10.4 ng/ml) compared with those with an acute course (n = 10, 3.9 ± 4.2 ng/ml, median; 2.7 ng/ml, P = 0.015). All 8 NBD patients with a chronic course underwent repeated CSF examination, and CSF BAFF levels significantly decreased after therapy (from 10.2 ± 4.0 ng/ml to 6.2 ± 3.6 ng/ml, P = 0.012, Wilcoxon's test), however, still remained high levels.

The results from the present study showed that BAFF levels in CSF were elevated in patients with NBD, and were independent of serum BAFF levels. It should be noted that NBD patients with progressive CNS manifestations such as psychosis and dementia showed significantly higher CSF BAFF levels compared with those with acute and transient CNS manifestations. In the present study, elevated BAFF levels were associated with NBD that presented with slowly progressive CNS manifestations. CSF IL-6 levels correlated with CSF cell counts, but no correlation was found between CSF BAFF levels and CSF cell counts. In addition, there was no association between BAFF and IL-6 levels. Therefore, IL-6 levels in NBD might reflect acute inflammation within the CNS caused by the presence of inflammatory cells, although the elevated levels may not be specific to the disease. Recent reports from experimental models highlight the possibility that inflammatory processes and cytokines in the brain contribute to the pathogenesis of mood disorders. BAFF transgenic mice show chronic inflammation in the CNS, impaired neurogenesis and an increased anxiety phenotype, similar to common clinical symptoms in NBD patients with a chronic course. Thus, elevated CNS BAFF levels were associated with NBD patients with a chronic course who presented progressive CNS manifestation such as psychosis and dementia.

CONCLUSION

Sustained elevation of BAFF levels in CSF reflect persistent CNS inflammation or damage, and might play an important role in the pathogenesis of progressive neuropsychiatric manifestations in NBD. This might be consistent with observations that NBD patients with a chronic course generally show poor responses to any form of immunosuppressive therapy. Thus, BAFF levels in CSF may be a good prognostic marker for NBD, especially in patients with a chronic disease course.