Research Article

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Concentrations of B cell-activating factor, aquaporin-4 antibody and brain-derived neurotrophic factor in neuromyelitis optica spectrum disorder

https://doi.org/10.1515/tjb-2022-0061
Received March 9, 2022; accepted July 22, 2022; published online September 19, 2022

Abstract

Objectives: To explore the correlations of B cell-activating factor (BAFF), aquaporin-4 antibody (AQP4-Ab) and brain-derived neurotrophic factor (BDNF) with the severity of neuromyelitis optica spectrum disorder (NMOSD).

Methods: Sixty-eight NMOSD patients were selected as an NMOSD group, and 65 patients with non-inflammatory neurological diseases hospitalized in the same period were selected as a control group. The severity of the disease was assessed using the expanded disability status scale (EDSS). Logistic regression analysis was conducted on the influencing factors for the severity of NMOSD. The correlations of BAFF, AQP4-Ab and BDNF with clinical characteristics were studied by Spearman’s analysis.

Results: The patients with EDSS score ≥7 points, number of involved spinal segments ≥5 and recurrence ≥3 times had a lower level of BAFF in the cerebrospinal fluid than the level of those with 4 points ≤ EDSS score <7 points, EDSS score <4 points, number of spinal segments <5 and recurrence <3 times (p<0.05). BAFF concentration was negatively correlated with disease duration, EDSS score, number of involved spinal segments and recurrence status (p<0.05). AQP4-Ab concentration was positively correlated with disease duration, EDSS score, number of involved spinal segments and recurrence status (p<0.05).

Conclusions: The concentrations of BAFF and AQP4-Ab in the cerebrospinal fluid can well predict the progression of NMOSD, correlated with the severity.

Keywords: aquaporin 4; B-cell activating factor; brain-derived neurotrophic factor; neuromyelitis optica; severity.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an uncurable autoimmune disease of the nervous system [1]. This disease selectively damages the optic nerve and spinal cord and gives repeated attacks causing different degrees of nervous system damage each time [2]. In the early stage, patients suffer from a diminution of vision, blurred vision, numbness, and weakness of limbs. In severe cases, blindness, paralysis, confusion, dizziness, headache and even respiratory failure may occur, threatening the patients’ life [3]. NMOSD mostly endangers the middle-aged population, especially females, typified by rapid progression, high disability and mortality rates, and poor prognosis. In addition, early immunosuppressive therapy is highly recommended due to the high morbidity rate associated with recurrence [4].

Aquaporin-4 antibody (AQP4-Ab) is an NMOSD-specific antibody, and the AQP4-Ab-positive result in the cerebrospinal fluid or serum is an important basis for diagnosing NMOSD [5]. The pathogenesis and etiology of NMOSD...
have been extensively studied [6–8]. AQP4-Ab may bind astrocyte AQP4 to activate complements, inducing a series of cytotoxic reactions, so astrocytes are damaged, and the blood-brain barrier permeability is increased. Then the damaged astrocytes and activated complement-producing cytokines mediate inflammatory cell infiltration, ultimately resulting in the demyelination of nerve fibers and neuronal necrosis or injury [9]. Additionally, B cell-activating factor (BAFF) is a key cytokine keeping the functional stability of B cells, which can help regulate innate and adaptive immune responses [10]. The expression of BAFF is significantly up-regulated in a variety of autoimmune diseases [11]. Moreover, brain-derived neurotrophic factor (BDNF), one of the important members of the neurotrophic factor family, is secreted by neuronal target cells and then nourishes neurons, which is crucial for neuronal growth, development, protection and repair [12].

Thereby motivated, the concentrations of BAFF, AQP4-Ab and BDNF in the serum and cerebrospinal fluid of NMOSD patients were detected in this study, and their correlations with the degree of disease progression were explored, aiming to provide a valuable basis for clinical diagnosis and treatment.

Materials and methods

General data

This study has been approved by the ethics committee of Sichuan Provincial People’s Hospital and written informed consent has been obtained from all patients. A total of 68 NMOSD patients admitted to our hospital from January 2021 to January 2022 were selected as an NMOSD group, including 12 males and 56 females aged 19–66 years old, with an average of (45.79 ± 11.28) years old. The disease duration was 1–16 years, with an average of (3.73 ± 1.52) years. Another 65 patients with non-inflammatory neurological diseases (intracranial hypotension syndrome, migraine and motor neuron disease) hospitalized in the same period were selected as a control group, including 14 males and 51 females aged 21–67 years old, with an average of (46.03 ± 11.07) years old. There were no significant differences in age or gender ratio between the two groups (p>0.05).

Inclusion criteria: (1) Patients meeting the diagnostic criteria for acute myelitis and optic neuritis in the “International Consensus Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorders” [13]; (2) those positive for serum AQP4-Ab and diagnosed as NMOSD. AQP4-Ab level was measured through visual fluorescence observation [7]; (3) those aged ≥18 years old; (4) those with abnormal lesions extending more than 3 vertebral segments shown in spinal cord MRI. Exclusion criteria: (1) Patients with mental or consciousness disturbance or dementia; (2) those with obvious infarct lesions or tumors in the brain; (3) those with cardio-cerebrovascular diseases; (4) those with severe liver or kidney dysfunction; (5) those with non-idiopathic inflammatory demyelinating immune diseases of the central nervous system caused by vasculitis, sarcoidosis or systemic lupus erythematosus.

Collection of clinical data

The patients’ age of initial onset, gender, duration of disease, number of involved spinal segments and recurrence status were recorded.

Expanded disability status scale (EDSS) assessment

The severity of the disease was assessed using EDSS to quantitatively analyze the patient’s visual, cerebral, brainstem sensory, cerebellar, pyramidal and other nervous system functions. Three experienced neurologists gave a score (0–10 points). According to previous literature [14], NMOSD was classified into three grades: mild (EDSS score 0–4 points), moderate (4 points ≤ EDSS score <7 points) and severe (EDSS score ≥7 points).

Detection of BAFF, AQP4-Ab and BDNF in the serum and cerebrospinal fluid

Blood and cerebrospinal fluid samples were collected in the fasting state on the second morning of admission. Fasting venous blood (4 mL) was centrifuged at 3,000 rpm for 10 min. The supernatant was harvested to detect the serum levels of BAFF, AQP4-Ab and BDNF by enzyme-linked immunosorbent assay in strict accordance with the instructions of the apparatus and kits. The kit for BAFF was purchased from R&D Systems (USA; Cat. No. IC1357P). The minimum BAFF detection concentration is <30 pg/mL, and the reproducibility and inter-assay coefficients of variation (CV) are both ≤10%. The kit for AQP4-Ab was bought from Linyi Azelasi Biotechnology Co., Ltd (China; Cat. No. EK-2222), with a quantitative detection range of 0.1–200 ng/mL. The reproducibility CV is ≤10%, and the inter-assay CV is ≤10%. The kit for BDNF was obtained from Wuhan Elabscience Biotechnology Co., Ltd. (China; Cat. No. E-ELN-H0010C), with a detection range of 0.313–20 ng/mL. The intra- and inter-plate CVs are both ≤10%. During blood sample collection, the maintenance dose of azathioprine was 2–3 mg/kg/day, and that of mycophenolate mofetil was 1,500–2,000 mg/day. Rituximab was given according to the frequency of memory B cells in the peripheral blood.

The cerebrospinal fluid (4 mL) was extracted by lumbar puncture, and the levels of BAFF, AQP4-Ab and BDNF were detected by enzyme-linked immunosorbent assay in strict accordance with the instructions of apparatus and kits.

Recurrence status was determined when AQP4-Ab antibody detection was positive, accompanied by clinical symptoms; stable disease was determined when the detection was negative in each test, without apparent clinical manifestations. The time-lapse from the last relapse/corticosteroid therapy was two months after diagnosis.

Statistical analysis

SPSS 22.0 software was used for statistical analysis. The count data were expressed as n (%) and subjected to the χ² test. The measurement data were expressed as (x ± s), and compared by the t-test between two
groups and by analysis of variance among groups. Spearman’s analysis explored the correlations of BAFF, AQP4-Ab and BDNF with clinical characteristics, and logistic regression analysis was conducted. No adjustment for multiple comparisons was made. p<0.05 was considered statistically significant.

Results

Concentrations of BAFF, AQP4-Ab and BDNF in the serum and cerebrospinal fluid

The levels of serum BAFF and BDNF had no significant differences between NMOSD and control groups (p>0.05), and the level of serum AQP4-Ab in the NMOSD group was high (Table 1).

The NMOSD group had a significantly lower level of BAFF in the cerebrospinal fluid than the control group (p<0.05). The level of BDNF in cerebrospinal fluid had no significant difference between NMOSD and control groups (p>0.05) (Table 2).

Concentrations of BAFF, AQP4-Ab and BDNF in the cerebrospinal fluid of patients with different clinical characteristics

The concentrations of BAFF and AQP4-Ab had no significant differences among the patients with different ages of initial onset, gender ratios and disease duration (p>0.05). No significant difference was found in the level of BDNF in the cerebrospinal fluid among the patients with different ages of initial onset, gender ratios, duration of disease, EDSS scores, number of involved spinal segments and recurrence status (p>0.05). The patients with EDSS score ≥7 points, number of involved spinal segments ≥5 and recurrence ≥3 times had a lower level of BAFF in the cerebrospinal fluid than the level of those with 4 points ≤EDSS score <7 points, EDSS score <4 points, number of involved spinal segments <5 and recurrence <3 times (p<0.05). The level of AQP4-Ab in the cerebrospinal fluid was higher in patients with EDSS score ≥7 points, number of involved spinal segments ≥5 and recurrence ≥3 times than that in patients with 4 points ≤EDSS score <7 points, EDSS score <4 points, number of involved spinal segments <5 and recurrence <3 times (p<0.05) (Table 3).

Logistic regression analysis results of the severity of NMO

Multivariate logistic regression analysis was conducted by using the number of involved spinal segments, recurrence status, BAFF, AQP4-Ab and BDNF as independent variables, and the severity of disease as a dependent variable [EDSS score <4 points (mild)=1, 4 points ≤EDSS score <7 points (moderate)=2, EDSS score ≥7 points (severe)=2]. The results showed that the number of involved spinal segments, recurrence status, BAFF and AQP4-Ab were influencing factors for the severity of NMOSD (Table 4).

Table 1: Concentrations of BAFF, AQP4-Ab and BDNF in serum (\(\bar{x} \pm s\)).

| Group           | n  | BAFF, pg/mL  | AQP4-Ab, ng/mL | BDNF, \(\mu g/L\) |
|-----------------|----|--------------|----------------|---------------------|
| Control group   | 65 | 224.03 ± 125.18 | –              | 6.03 ± 0.87         |
| NMOSD group     | 68 | 246.34 ± 124.92 | 62.53 ± 6.17   | 5.19 ± 0.49         |
| t               |    | 2.336         | –              | 2.967               |
| p               |    | 0.119         | –              | 0.094               |

AQP4-Ab, aquaporin-4 antibody; BAFF, B cell-activating factor; BDNF, brain-derived neurotrophic factor; NMOSD, neuromyelitis optica spectrum disorder.

Table 2: Concentrations of BAFF, AQP4-Ab and BDNF in cerebrospinal fluid (\(\bar{x} \pm s\)).

| Group           | n  | BAFF, pg/mL  | AQP4-Ab, ng/mL | BDNF, \(\mu g/L\) |
|-----------------|----|--------------|----------------|---------------------|
| Control group   | 65 | 508.53 ± 224.26 | –              | 0.18 ± 0.01         |
| NMOSD group     | 68 | 152.07 ± 78.42 | 38.42 ± 4.71   | 0.16 ± 0.02         |
| t               |    | 31.758       | –              | 1.712               |
| p               |    | <0.001       | –              | 0.146               |

AQP4-Ab, aquaporin-4 antibody; BAFF, B cell-activating factor; BDNF, brain-derived neurotrophic factor; NMOSD, neuromyelitis optica spectrum disorder.
Table 3: Concentrations of BAFF, AQP4-Ab and BDNF in cerebrospinal fluid of patients with different clinical characteristics (̄x ± s).

| Item                        | n   | BAFF, pg/mL  | t    | p    | AQP4-Ab, ng/mL | t/F | p    | BDNF, μg/L | t    | p-Value |
|-----------------------------|-----|--------------|------|------|----------------|-----|------|------------|------|---------|
| Age of initial onset        |     |              |      |      |                |     |      |            |      |         |
| ≥40 years                   | 31  | 151.13 ± 77.64 | 1.734 | 0.183 | 38.64 ± 5.03   | 1.362 | 0.215 | 0.17 ± 0.01 | 1.127 | 0.301   |
| <40 years                   | 37  | 152.92 ± 78.93 |      |      | 37.19 ± 4.64   |     |      |            |      |         |
| Gender                      |     |              |      |      |                |     |      |            |      |         |
| Male                        | 12  | 151.46 ± 78.84 | 1.337 | 0.206 | 37.17 ± 5.09   | 1.157 | 0.307 | 0.16 ± 0.02 | 1.435 | 0.213   |
| Female                      | 56  | 152.75 ± 78.05 |      |      | 38.52 ± 4.62   |     |      |            |      |         |
| Duration of disease         |     |              |      |      |                |     |      |            |      |         |
| ≥3 years                    | 40  | 152.39 ± 79.04 | 1.296 | 0.211 | 39.32 ± 4.39   | 1.743 | 0.134 | 0.17 ± 0.02 | 1.012 | 0.329   |
| <3 years                    | 28  | 151.42 ± 78.17 |      |      | 37.27 ± 5.13   |     |      |            |      |         |
| EDSS score                  |     |              |      |      |                |     |      |            |      |         |
| ≥7 points                   | 32  | 147.56 ± 79.24 | 9.314 | <0.001 | 43.18 ± 4.57   | 5.719 | <0.001 | 0.16 ± 0.01 | 2.174 | 0.098   |
| 4 points ≤EDSS <7 points    | 21  | 152.24 ± 10.56 |      |      | 41.67 ± 4.83   |     |      |            |      |         |
| <4 points                   | 15  | 159.73 ± 69.37 |      |      | 37.73 ± 5.02   |     |      |            |      |         |
| Number of involved spinal segments | |         |      |      |                |     |      |            |      |         |
| ≥5                          | 41  | 144.89 ± 81.46 | 15.28 | <0.001 | 42.92 ± 5.03   | 4.982 | 0.004 | 0.17 ± 0.01 | 2.048 | 0.087   |
| <5                          | 27  | 162.37 ± 67.51 |      |      | 37.83 ± 4.62   |     |      |            |      |         |
| Recurrence status           |     |              |      |      |                |     |      |            |      |         |
| ≥3 times                    | 33  | 146.93 ± 81.16 | 12.62 | <0.001 | 42.07 ± 4.94   | 4.473 | 0.006 | 0.15 ± 0.02 | 2.517 | 0.079   |
| <3 times                    | 35  | 161.73 ± 70.08 |      |      | 37.22 ± 4.27   |     |      |            |      |         |

AQP4-Ab, aquaporin-4 antibody; BAFF, B cell-activating factor; BDNF, brain-derived neurotrophic factor; EDSS, expanded disability status scale; NMOSD, neuromyelitis optica spectrum disorder.

Table 4: Logistic regression analysis results of severity of NMOSD.

| Parameter                               | Regression coefficient | Standard error | Wald χ² | OR     | 95%CI     | p-Value   |
|-----------------------------------------|------------------------|----------------|---------|--------|-----------|-----------|
| Number of involved spinal segments ≥5   | 0.513                  | 0.142          | 8.795   | 1.766  | 1.313–4.519| <0.001    |
| Recurrence ≥3 times                     | 0.408                  | 0.127          | 6.714   | 1.375  | 1.015–2.916| <0.001    |
| BAFF, pg/mL                             | 0.172                  | 0.107          | 3.829   | 0.937  | 0.514–1.037| 0.012     |
| AQP4-Ab, ng/mL                          | 0.428                  | 0.174          | 7.962   | 3.519  | 1.038–4.925| <0.001    |
| BDNF, μg/L                              | 0.912                  | 1.736          | 1.137   | 2.147  | 0.714–11.284| 0.637     |

AQP4-Ab, aquaporin-4 antibody; BAFF, B cell-activating factor; BDNF, brain-derived neurotrophic factor; CI, confidence interval; NMOSD, neuromyelitis optica spectrum disorder; OR, odds ratio.

Correlations of BAFF, AQP4-Ab and BDNF with clinical characteristics

According to Spearman’s analysis, the concentrations of BAFF and AQP4-Ab in the cerebrospinal fluid of NMOSD patients were not correlated with the age of initial onset, gender, or disease duration (p>0.05). The concentration of BDNF had no correlations with the age of initial onset, gender, duration of disease, EDSS score, number of involved spinal segments or recurrence status (p>0.05). The concentration of BAFF was negatively correlated with the duration of disease, EDSS score, number of involved spinal segments and recurrence status (p<0.05), and AQP4-Ab concentration was positively correlated with the duration of disease, EDSS score, number of involved spinal segments and recurrence status (p<0.05) (Table 5).

Discussion

NMOSD is an autoimmune disease of the central nervous system, which mainly invades the optic nerve and spinal
Table 5: Correlations of BAFF, AQP4-Ab and BDNF with clinical characteristics.

| Item                        | BAFF, pg/mL | AQP4-Ab, ng/mL | BDNF, pg/L |
|-----------------------------|-------------|----------------|------------|
|                             | r           | p-Value        | r           | p-Value        | r           | p-Value        |
| Age of initial onset, year  | −0.183      | 0.279          | 0.196       | 0.132          | −0.203      | 0.164          |
| Gender                      | −0.064      | 0.582          | 0.079       | 0.613          | −0.179      | 0.237          |
| Duration of disease, year   | −0.264      | 0.116          | 0.183       | 0.156          | −0.064      | 0.693          |
| EDSS score (point)          | −0.719      | <0.001         | 0.713       | <0.001         | −0.276      | 0.096          |
| Number of involved spinal segments | −0.573      | <0.001         | 0.636       | <0.001         | −0.218      | 0.134          |
| Recurrence status           | −0.628      | <0.001         | 0.695       | <0.001         | −0.177      | 0.108          |

AQP4-Ab, aquaporin-4 antibody; BAFF, B cell-activating factor; BDNF, brain-derived neurotrophic factor; EDSS, expanded disability status scale.

NOMOSD patients are generally complicated with other autoimmune diseases, so they are prone to recurrence. NOMOSD is primarily manifested as various degrees of visual and motor dysfunction, pain, sensory disturbance, and spasm of limbs and trunk [16]. The patients with recurrent NOMOSD have an unsatisfactory prognosis, and about 70% suffer from severe paralysis, diminution of monocular vision or even blindness within 5 years, seriously affecting the quality of life [17]. A variety of cytokines and inflammatory cells, including B cells, play important roles in the onset and progression of NOMOSD [18]. This disease is mainly treated by controlling the inflammation caused by an acute inflammatory response and preventing recurrence. Hence, early diagnosis and reasonable intervention are necessary for ameliorating the symptoms and prognosis of patients.

As a member of the tumor necrosis factor ligand superfamily, BAFF is a key factor for facilitating the development, differentiation and maturation of B cells. It can maintain the structure of the germinal center of lymphoid tissues and enhance the synthesis of immunoglobulins [19]. The important roles of BAFF in autoimmune diseases such as rheumatoid arthritis [20] and myasthenia gravis [21] are well-documented. In the present study, no significant difference was found in the concentration of serum BAFF between the control and NOMOSD groups. Still, the level of BAFF in the cerebrospinal fluid was significantly lower in the NOMOSD group than in the control group. The patients with EDSS score ≥7 points, number of involved spinal segments ≥5 and recurrence ≥3 times had a lower level of BAFF in the cerebrospinal fluid than the level of those with 4 points ≤ EDSS score <7 points, EDSS score <4 points, number of involved spinal segments <5 and recurrence <3 times. The concentration of BAFF was negatively correlated with the duration of disease, EDSS score, number of involved spinal segments and recurrence status. Thus, we postulated that BAFF essentially participated in NOMOSD, consistent with a previous study [22]. Additionally, the level of BAFF in the cerebrospinal fluid may work as a biomarker for the differential diagnosis of NOMOSD and multiple sclerosis [23].

AQP4 is a transmembrane protein distributed mainly in the perivascular space, cerebral microvessels and pia mater. It is mainly related to NOMOSD as an auxiliary marker for the early diagnosis of NOMOSD [24]. Wang et al. reported that 84.9% of NOMOSD patients were positive for AQP4-Ab in the serum [25]. In this study, the level of AQP4-Ab in the cerebrospinal fluid was higher in patients with an EDSS score ≥7 points, number of involved spinal segments ≥5 and recurrence ≥3 times than that in patients with 4 points ≤ EDSS score <7 points, EDSS score <4 points, number of involved spinal segments <5 and recurrence <3 times. Moreover, AQP4-Ab concentration was positively correlated with the duration of disease, EDSS score, number of involved spinal segments and recurrence status. Consistent with previous literature [26], AQP4-Ab is of great significance to the occurrence and progression of NOMOSD.

BDNF exerts crucial effects on the growth and development of the central nervous system, the differentiation of central and peripheral nervous systems, and the maintenance of normal physiological functions [27]. It also has neuroprotective effects on autoimmune inflammatory diseases such as multiple sclerosis [28]. In this study, the levels of BDNF in the serum and cerebrospinal fluid had no differences between NOMOSD and control groups and had no significant correlations with clinical characteristics. Finally, the results of multivariate logistic regression analysis revealed that the number of involved spinal segments, recurrence status, BAFF and AQP4-Ab were influencing factors for the severity of NOMOSD. BAFF and AQP4-Ab can be used as important predictors for the severity of NOMOSD.
Conclusions

In conclusion, the concentrations of BAFF and AQP4-Ab in the cerebrospinal fluid can well predict the progression of NMOSD, being associated with the severity of the disease. Possibly, the absence of correlation between BDNF concentration and disease severity can be ascribed to the small sample size of this study. Therefore, studies with larger sample sizes are required in the future to validate the findings further herein.

Research funding: This study was financially supported by the Key Research Project of Science & Technology Department of Sichuan Province (No. 2021YFS0131 and 2020YFS0414).

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Conflict of interest: The authors declare no conflict of interest.

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