RESEARCH ARTICLE

Serum levels of cell adhesion molecules in patients with neuromyelitis optica spectrum disorder

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Abstract

Objectives: Blood–brain barrier (BBB) disruption is a critical pathological process involved in neuromyelitis optica spectrum disorder (NMOSD). Here, we characterized the profile of five cell adhesion molecules in patients with NMOSD.

Methods: We measured levels of cell adhesion molecules, including ICAM-1, ICAM-2, VCAM-1, PECAM-1, and NCAM-1, in the serum of 28 patients with NMOSD, 24 patients with multiple sclerosis (MS), and 25 healthy controls (HCs).

Results: ICAM-2 levels (median: 394.8 ng/mL) were increased in patients with NMOSD compared with MS (267.1 ng/mL, \( P = 0.005 \)) and HCs (257.4 ng/mL, \( P = 0.007 \)), and VCAM-1 and ICAM-1 levels were higher in patients with NMOSD (641.9 ng/mL and 212.7 ng/mL, respectively) compared with HCs (465 ng/mL \( P = 0.013 \) and 141.8 ng/mL \( P = 0.002 \), respectively). However, serum PECAM-1 levels were lower in patients with NMOSD (89.62 ng/mL) compared with MS (106.9 ng/mL, \( P = 0.015 \)) and HCs (107.2 ng/mL, \( P = 0.007 \)). Receiver operating characteristic curve analysis revealed that PECAM-1 (area under the curve (AUC): 0.729) and ICAM-2 (AUC: 0.747) had adequate abilities to distinguish NMOSD from MS, and VCAM-1 (AUC: 0.719), PECAM-1 (area under the curve: 0.743), ICAM-1 (AUC: 0.778), and ICAM-2 (AUC: 0.749) exhibited potential to differentiate NMOSD and HCs. Serum levels of PECAM-1 also demonstrated a negative correlation with Kurtzke Expanded Disability Status Scale scores in patients with NMOSD.

Interpretation: Our results reveal possible BBB breakdown signals specifically observed in NMOSD and highlight the potential role of cell adhesion molecules as biomarkers of this disease.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS) are immune-mediated neuroinflammatory diseases of the central nervous system (CNS). Clinically differentiating these two diseases is critical because their therapeutic regimens vary and a few medications for MS may exacerbate NMOSD.1 Following the discovery of anti–aquaporin 4 antibody (AQP4-IgG) in patients with NMOSD, clinicians now consider these two diseases to be distinct entities with potentially different pathomechanisms.2–4 AQP4 is a water channel protein primarily expressed in astrocyte foot processes, which form the glia limitans of the blood–brain barrier (BBB).5 Circulating AQP4-IgGs enter the brain through BBB leakage and initiate complement- and antibody-dependent cytotoxic cascades by binding to AQP4, which leads to profound infiltration of lymphocytes, macrophages, and eosinophils as well as extensive destruction in the diencephalon, periependymal regions, area postrema, and spinal cords in patients with NMOSD.6,7 AQP4-IgG is considered a highly specific biomarker for NMOSD; however, 20–30% of patients with NMOSD do not exhibit AQP4-IgGs, which hampers efforts to distinguish NMOSD from MS in these patients. Therefore, other biomarkers

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are required for discriminating between NMOSD and MS.

BBB disruption is a hallmark of NMOSD that has been demonstrated in magnetic resonance imaging (MRI) with gadolinium contrast-enhanced lesions, particularly in the acute stage of NMOSD.6,8,9 BBB destruction is essential for AQP4-IgGs to enter the CNS.9-11 BBB breakdown regulates the expression of endothelial cell adhesion molecules that tightly mediate immune cell extravasation and trafficking into the CNS as well as contribute to modulation of vascular integrity.12,13 Endothelial cell adhesion molecules such as vascular cell adhesion molecule-1 (VCAM1), intracellular adhesion molecule-1 (ICAM1), intracellular adhesion molecule-2 (ICAM2), platelet endothelial cell adhesion molecule-1 (PECAM1), and neural cell adhesion molecule-1 (NCAM1) belong to the immunoglobulin superfamily.14 Studies have suggested that VCAM1, ICAM1, and PECAM1 are instrumental in BBB disruption for transmigration of activated peripheral lymphocytic cells to the CNS.6,12,13,15

In MRI, NMOSD is characterized by longitudinally extensive gadolinium contrast-enhanced lesions at the spinal cord and/or optic nerves, whereas periventricular plaques with partial ring enhancement are frequently observed in MS.16 The differences in patterns and distributions of contrast-enhanced lesions suggest these two diseases generate different BBB breakdown patterns. The discovery of BBB-reactive antibodies, such as GRP78 antibodies in NMOSD and galactin-3 antibodies in MS, further implies that the BBB breakdown mechanisms differ between these two neuroinflammatory diseases.6,16 Although the exact role of BBB breakdown in the pathogenesis of NMOSD remains elusive, cell adhesion molecules may represent BBB function and serve as disease activity biomarkers for many neuroinflammatory diseases of the CNS.5,9,17 Therefore, we evaluated the profile of five cell adhesion molecules, ICAM1, ICAM2, VCAM1, PECAM1, and NCAM1, in patients with NMOSD. The levels of these molecules were subsequently compared with those in patients with MS and healthy controls (HCs).

**Materials and methods**

**Ethics approval and consent to participate**

The collection of venous blood from enrolled patients was approved by the Institutional Review Board of Chang Gung Memorial Hospital (ethical license No: 20130226033D001 and 201701423B0). Informed consents were obtained from all participants in this study.

**Patient recruitment**

This is a cross-sectional study from 1 January 2014, to 31 December 2019, in Chang Gung Memorial Hospital-Linkou Medical Center in Taiwan. Patients from the neurology ward diagnosed with NMOSD or MS by two experienced specialists in neuroimmunology (LS Ro and KH Chang) according to the international consensus diagnostic criteria for NMOSD18 and the McDonald criteria,19 respectively, were recruited. Both AQP-4 IgG positive and negative were eligible for the study. No participant had systemic infection, chronic renal failure, cardiac or liver dysfunction, malignancies, or autoimmune diseases other than NMOSD and MS. Healthy controls were recruited from neurology outpatient clinics by a convenience sample of individuals seen at the time of recruitment, and were frequency matched for sex and age of patients.

**Sample collection**

Venipunctures were performed on all participants. Blood samples of the patients with NMOSD and MS were collected within 2 weeks after symptom onset or acute relapses of the disease. All samples were obtained before treatment with corticosteroids, intravenous immunoglobulins, or plasmapheresis. Blood samples were maintained at room temperature for 30 min and then centrifuged at 1000–2000 g for 10 min. Serum was carefully collected from the supernatant, aliquoted, frozen at −80°C, and stored until analysis.

The neurological disability of the patients at the time of venipuncture was assessed using the Kurtzke Expanded Disability Status Scale (EDSS).20

**Enzyme-linked immunosorbent assays for quantification of cell adhesion molecule expression in serum**

We used enzyme-linked immunosorbent assay kits to evaluate the serum levels of VCAM1 (R&D), PECAM1 (R&D), NCAM1 (RayBio), ICAM1 (R&D), and ICAM2 (MyBioSource). Each assay was measured in duplicate for each sample at the same time.

**Statistical analysis**

Prism 8 (GraphPad) was used for statistical analyses. The D’Agostino–Pearson test21,22 revealed that ICAM1, ICAM2, VCAM1, PECAM1, and NCAM1 levels were not normally distributed. Therefore, the Kruskal–Wallis test (nonparametric test to compare unmatched groups) was applied to compare the differences in these noncategorical variables among the NMOSD, MS, and HC groups. For the variables with significant differences among NMOSD,
MS, and HCs, namely ICAM1, ICAM2, VCAM1, and PECAM1. Spearman correlation was applied to evaluate the relationship between their levels and the EDSS at the time of sample collection. Data are expressed as median, interquartile range (IQR), and 95% confidence interval (CI). All P values were two-tailed, and P < 0.05 was considered significant. Variables with significant differences among NMOSD, MS, and HCs were further analyzed using receiver operating characteristic (ROC) curves. Area under the ROC curve (AUC) analysis was applied for distinguishing those with NMOSD from those with MS and HCs. Using receiver operating characteristic (ROC) curves, area among NMOSD, MS, and HCs were further analyzed and found to be significant. Variables with significant differences among NMOSD, MS, and HCs were further analyzed under the ROC curve (AUC) analysis was applied for distinguishing those with NMOSD from those with MS, and ICAM1 (AUC = 0.777, 95% CI: 0.654–0.901, P = 0.001, Fig. 1B), ICAM2 (AUC = 0.749, 95% CI: 0.617–0.88, P = 0.002, Fig. 2D), VCAM1 (AUC = 0.719, 95% CI: 0.578–0.859, P = 0.006, Fig. 2F) and PECAM1 (AUC = 0.743, 95% CI: 0.608–0.878, P = 0.003, Fig. 2H) demonstrated adequate potential to distinguish patients with NMOSD from HCs. We further analyzed the correlation between the serum levels of ICAM1, ICAM2, VCAM1, or PECAM1 and disease severity, which was evaluated using the EDSS at sample collection (Fig. 3). The results revealed a significant correlation between serum levels of PECAM1 and EDSS score in patients with NMOSD (r = −0.569, P = 0.002, Fig. 3D). However, serum levels of ICAM1 (r = −0.088, Fig. 3A), ICAM2 (r = −0.016, Fig. 3B), and VCAM1 (r = −0.045, Fig. 3C) did not demonstrate correlations with EDSS score.

### Discussion

The immunoglobulin superfamily of cell adhesion molecules, including ICAM1, ICAM2, VCAM1, PECAM1, and

#### Table 1. Clinical characteristics of the patients with NMOSD, MS, and HCs

| Parameter               | NMOSD (n = 28) | MS (n = 24) | HC (n = 25) |
|-------------------------|---------------|-----|-----------|
| Sex (female/male)       | 23/5          | 16/8| 17/8      |
| Age (years)             | 47.86 ± 15.16 | 39.96 ± 14.51 | 47.96 ± 14.09 |
| Age at onset (years)    | 45.82 ± 13.59 | 37.83 ± 13.81 |           |
| EDSS                    | 4.27 ± 1.90   | 3.31 ± 1.43 |           |
| LESCL (%)               | 20 (72.43)    | 0 (0)      |           |
| ON (%)                  | 6 (21.43)     | 2 (8.33)   |           |
| APS (%)                 | 2 (7.14)      | 0 (0)      |           |
| AQP4-IgG (%)            | 26 (92.86)    | 0 (0)      |           |
| Lesion(s) with gadolinium enhancement (%) | 23 (82.14) | 19 (79.17) | |

All blood samples were collected from patients with NMOSD and MS within 2 weeks after symptom onset or acute relapse of disease and before their treatment with corticosteroids, intravenous immunoglobulins, or plasmapheresis.

APS: area postrema syndrome; AQP4-IgG: anti-aquaporin 4 antibody; EDSS: Kurtzke Expanded Disability Status Scale; HC: healthy control; LESCL: longitudinally extensive spinal cord lesion; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder; ON: optic neuritis.

*Statistically significant difference compared with MS, P < 0.05.
NCAM1, are constitutional proteins expressed on endothelial cells, leukocytes, epithelial cells, and fibroblasts when the BBB is intact. These cell adhesion molecules, which are upregulated by proinflammatory factors, play essential roles in leukocyte-endothelial interaction and regulation of the neuroinflammatory cascade of immunemediated CNS diseases by modulating vascular permeability and BBB integrity. Increases of cell adhesion molecules in cerebrospinal fluid (CSF) or shedding into serum may be associated with BBB damage. The dysregulation of cell adhesion molecules and disruption of the BBB lead to penetration of inflammatory cells and immunoglobulins into the CNS. Patients with NMOSD exhibited a significant increase in serum ICAM2 compared with those with MS and HCs, an increase in serum VCAM1 and ICAM1 compared with HCs, but a significant decrease in serum PECAM1, with a negative correlation to disease severity. These markers also demonstrated potential for discriminating NMOSD from MS and HCs, suggesting these molecules might be candidate biomarkers for NMOSD.

Figure 1. Serum levels of (A) ICAM1, (B) ICAM2, (C) VCAM1, (D) PECAM1, and (E) NCAM in patients with neuromyelitis optica spectrum disorder (NMOSD, n = 28), multiple sclerosis (MS, n = 24), and healthy controls (HCs, n = 25). Box-whisker plots depict the median and interquartile range (IQR) of each group. Error bars represent 95% confidence intervals. Statistically significant differences between two groups: *P < 0.05, **P < 0.01, ***P < 0.001
VCAM1, suggesting that PECAM1 plays a different role from other cell adhesion molecules in NMOSD. The negative correlation between PECAM1 levels and EDSS further suggests the protective role of PECAM1 in the pathogenesis of NMOSD. ICAM2 is highly expressed on endothelial cells, platelets, and various leukocytes. Endothelial ICAM2 is involved in the maturation of endothelial junctions and adhesion of leukocytes to the endothelium. ICAM2 also contributes to neutrophil crawling and the initiation of paracellular diapedesis.

Figure 2. Receiver operating characteristic (ROC) curve for serum levels of ICAM1 (A-B), ICAM2 (C-D), VCAM1 (E-F), and PECAM1 (G-H) to distinguish patients with neuromyelitis optica spectrum disorder (NMOSD) from those with multiple sclerosis (MS) and healthy controls (HCs). AUC: area under the ROC curve

Figure 3. Correlations between serum levels of (A) ICAM1, (B) ICAM2, (C) VCAM1, or (D) PECAM1, and Kurtzke Expanded Disability Status Scale (EDSS) score in patients with neuromyelitis optica spectrum disorder (NMOSD). r: spearman correlation coefficient
Neutrophil binding to endothelial ICAM2 increases vascular permeability during acute neuroinflammatory processes. The high level of ICAM2 in NMOSD suggests its role in BBB breakdown in NMOSD. The different levels of PECAM1 and ICAM2 evident between NMOSD and MS further indicate distinct immunopathogenesis of these two diseases.

By binding to μ4 integrin/very late antigen-4 and leukocyte function–associated antigen 1, VCAM1 and ICAM1 promote transendothelial recruitment of immune cells and the subsequent neuroinflammatory cascade. Uzawa et al. revealed that patients with NMOSD exhibit significantly higher CSF levels of ICAM1 and VCAM1 than do patients with MS. Our results further revealed increased ICAM1 and VCAM1 serum levels in those with NMOSD compared with HCs. Consistent with Uzawa’s findings, serum levels of ICAM1 and VCAM1 in our study were not different between those with MS and HCs, implying that MS exhibits different mechanisms of BBB disruption and neuroinflammatory pathogenesis from NMOSD.

Studies have suggested that the involvement of NCAM1 in cell–cell adhesion, axonal fasciculation and outgrowth, synaptic plasticity, myelination, and remyelination has a role in the reparative mechanisms of myelin in MS. An elevated NCAM1 level was also reported in MS. However, none of the data were related to NMOSD. In the current study, we did not find significant changes of NCAM1 levels between patients with NMOSD, MS, and HCs. Studies have revealed that serum VCAM1, ICAM1, and PECAM1 levels are elevated in MS and correlate with gadolinium-enhanced MRI lesions. By contrast, lower serum VCAM1 and PECAM1 levels in patients with optic neuritis who tend to develop MS were reported by Kalinowska-Lyszczarz et al. We did not find significant differences in VCAM1, PECAM1, ICAM1, ICAM2, and NCAM1 levels between those with MS and HCs.

A possible explanation for the variable serum levels of these cell adhesion molecules among those with NMOSD, MS, and HCs is that these molecules might have different pro- or anti-inflammatory roles in maintaining and regulating the vascular integrity of the BBB during neuroinflammatory processes. Another potential reason is that the immunopathogenesis of NMOSD and MS is distinct, leading to the involvement of different adhesion-induced signaling and BBB-reactive autoantibodies.

This study had some limitations. The evolving diagnostic criteria for NMOSD and MS may explain the difference between our results and those of previous reports. Our sample size was also relatively small. The low number of AQP4-IgG-negative patients also limits the generalization of our results to this subpopulation of patients with NMOSD. Although not significantly different, the younger age in patients with MS in our study may have affected adhesion molecule levels. The CSF levels of these adhesion molecules were not available, and the details of their pathogenesis in NMOSD remained unknown. Nevertheless, our findings still highlight a new avenue in biomarker research in NMOSD.

Conclusions

In conclusion, our study demonstrated significantly higher levels of ICAM1, ICAM2, and VCAM1 and a lower level of PECAM1 in the serum of patients with NMOSD. These cell adhesion molecules could be potential biomarkers for distinguishing patients with NMOSD from those with MS and HCs. Furthermore, PECAM1 serum level could reflect clinical severity with a significantly negative correlation. These observations demonstrate a unique regulatory pattern of cell adhesion molecules in NMOSD.

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Conflicts of interest

None.

Author contribution

Kuo-Hsuan Chang and Long-Sun Ro contributed to conceptualization. Yan-Shi Lo and Bao-Luen Chang contributed to data curation. Kuo-Hsuan Chang and Bao-Luen Chang contributed to formal analysis. Kuo-Hsuan Chang contributed to funding acquisition. Kuo-Hsuan Chang and Bao-Luen Chang contributed to methodology. Kuo-Hsuan Chang, Long-Sun Ro, Chung-Mei Chen, Rong-Kuo Lu, Hong-Chou Kuo, Ming-Feng Liao, Chun-Wei Chang, Hong-Shiu Chang, Ching-Chang Huang, Yih-Ru Wu, Chun-Che Chu and Yi-Ching Weng contributed to resources. Kuo-Hsuan Chang contributed to...
supervision. Bao-Luen Chang and Kuo-Hsuan Chang contributed to writing – original draft. Kuo-Hsuan Chang, Bao-Luen Chang and Long-Sun Ro contributed to writing – review & editing.

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