


BRIEF COMMUNICATION

Clinical significance of soluble adhesion molecules in anti-NMDAR encephalitis patientsYuewen Ding^{1,2,a}, Chengjia Yang^{3,4,a}, Zheyi Zhou^{4,5,a}, Yu Peng¹, Jinyu Chen¹, Suyue Pan¹, Hong Xu⁴, Yuping Cai⁶, Kaiyun Ou⁷, Wei Xie^{2,8} & Honghao Wang¹ ¹Department of Neurology, Nanfang Hospital, Southern Medical University, Guangzhou, China²School of Traditional Chinese Medicine, Southern Medical University, Guangzhou, China³Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangdong Mental Health Center, Guangzhou, China⁴The Second School of Clinical Medicine, Southern Medical University, Guangdong Province, China⁵Department of Neurology, Liuzhou Traditional Chinese Medical Hospital, Liuzhou, China⁶Hexian Memorial Hospital, Guangzhou, China⁷Department of Neurology, Laibin People's Hospital, Laibin, China⁸Department of Traditional Chinese Medicine, Nanfang Hospital, Southern Medical University, Guangzhou, China**Correspondence**

Honghao Wang, Department of Neurology, Nanfang Hospital, Southern Medical University, 1838 North Guangzhou Avenue, Guangdong Province, Guangzhou 510515, China. Tel: 86-(020)62787664; Fax: 86-(020)72787664; E-mail: wang_whh@163.com and

Wei Xie, Department of Traditional Chinese Medicine, Nanfang Hospital, Southern Medical University, 1838 North Guangzhou Avenue, Guangzhou 510515, China. Tel: 86-(020)61641671; Fax: 86-(020)61641671; E-mail: xieweizn@fimmu.com

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^aThe authors contribute equally to this paper.

Abstract

Increasing evidence indicates that immune system dysfunction affects anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. This study aims to investigate the relationship between adhesion molecules and the pathophysiology in anti-NMDAR encephalitis. Soluble forms of Intercellular adhesion molecule-1 (sICAM-1), vascular adhesion molecule-1 (sVCAM-1), and L-selectin (sL-selectin), were measured in the CSF and serum of 26 participants with anti-NMDAR encephalitis, 11 patients with schizophrenia and 22 patients with noninflammatory disorders. CSF levels of sICAM-1, sVCAM-1 and sL-selectin were significantly elevated in the anti-NMDAR encephalitis group. sVCAM-1 levels were positively associated with modified Rankin scale score in anti-NMDAR encephalitis patients at the onset and 3-month follow-up.

Introduction

Anti-N-Methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder with diverse psychiatric and neurological features, most commonly psychosis, disorientation, amnesia, seizures, and a complex movement disorder.¹ This condition is most common in young women with or without tumors (ovarian teratoma usually).² Most patients with anti-NMDAR encephalitis develop a multistage illness that progresses from psychosis, memory deficits, seizures, speech disorder, movement disorder, autonomic symptoms, and central hypoventilation.³

The compromise of blood-brain barrier (BBB) integrity is closely related to the progression of autoimmune diseases.^{4,5} Adhesion molecules facilitate the process of leukocyte migration and further modulate the permeability of the BBB to immune cells.^{6–8} Intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), and L-selectin engaged with leukocyte integrins activates diverse signaling pathways in endothelial cells, result in the reorganization of junction complexes further mediate leukocyte adhesion migration.^{7,9}

ICAM-1 (CD54) is a transmembrane protein that is upregulated on endothelial and epithelial cells at sites of inflammation. It mediates the vascular adhesion and paracellular migration of leukocytes expressing activated LFA-1 (CD11a) and Mac-1 (CD11b). Soluble ICAM-1 promotes angiogenesis and serves an indicator of vascular endothelial cell activation or damage. VCAM-1 (CD106) is induced in endothelial cells by inflammatory cytokines including TNF- α and IL-1 β . This induces clustering of VCAM-1 and activation of intracellular signaling pathways that induce phosphorylation of tight junction proteins, resulting in their disassembly and redistribution from the cell border.¹⁰ L-selectin (Leukocyte Selectin, CD62L) is a cell surface glycoprotein expressed constitutively on a wide variety of leukocytes.¹¹ Acting in cooperation with P-selectin and E-selectin, L-Selectin mediates the initial interaction of circulating leukocytes on the endothelium.⁹ This initial interaction, also involving ICAM-1 and VCAM-1, leads eventually to extravasation of the white blood cell through the blood vessel wall into the extracellular matrix tissue. The majority of myeloid cells, B cells and virgin T cells express L-selectin, cleavage of L-selectin from the cell surface results in a high circulating level of functionally active soluble L-selectin.⁶ Multiple studies indicated that L-selectin, P-selectin E-selectin collaborate to mediate the initial binding of leukocytes to endothelium at sites of tissue injury and inflammation.^{12–14}

We have reported several inflammatory indicators or immune-modulate factors highly expressed in cerebrospinal fluid (CSF) or serum of patients with Anti-NMDAR encephalitis,^{15,16} but the profiles of molecules

facilitate the cells migration remain unclear. In this study, we measured the expression of soluble forms of ICAM-1 (sICAM-1), VCAM-1 (sVCAM-1), and L-selectin (sL-selectin) in patients with anti-NMDAR encephalitis. We also examined whether the soluble forms of these cell adhesion molecules can be measured as a diagnose or prognosis biomarker for anti-NMDAR encephalitis.

Methods and Materials

Subjects and behavioral assessments

Fifty-nine study participants aged between 9 and 60 years were recruited in this study. Participants consisted of 26 patients with anti-NMDAR encephalitis, 11 Schizophrenia (SP) and 22 noninflammation diseases (NID) control patients. The diagnosis of anti-NMDAR encephalitis was confirmed using revised anti-NMDAR encephalitis diagnosis criteria of 2016,¹⁷ including the presence of clinical manifestations and detection of anti-NMDAR antibodies in the CSF. Patients met DSM-IV criteria for SP were recruited. NID controls including 16 cases of cerebrovascular disease and six cases of movement disorders. Both the SP and NID control groups were negative for specific CSF and serum antibodies.

CSF and serum samples in this study were obtained from patients within 3 days of their admission, nine pair of CSF and serum samples from patients with NMDAR encephalitis were collected at 3-month follow-up. Patients with anti-NMDAR encephalitis received evaluation of neurological condition using modified Rankin scale (mRS) scores both at admission and 3-month follow-up after discharge.

The study protocol was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University, each participant provided written informed consent to participate. A detailed medical history was obtained from all patients.

Measurement of sICAM-1, sVCAM-1, and sL-selectin

CSF samples were collected using polypropylene tubes and centrifuged at 4000g for 10 min. Blood samples were collected using BD Vacutainer Serum Separation tubes and let clot for 20 min at room temperature. Sera were centrifuged at 2000g for 10 min and stored at -80°C until the assay. Levels of sICAM-1 were determined with sICAM-1 Quantikine ELISA kits (R&D Systems) with sensitivities of 0.254 ng/mL. Levels of VCAM-1 were determined with sVCAM-1 Quantikine ELISA kits (R&D Systems) with sensitivities of 1.26 ng/mL. Levels of sL-selectin were determined with sL-selectin ELISA Kit (Abnova) with sensitivities of 0.195 ng/mL. The assays

were performed according to the protocols recommended by the manufacturers. All standards and samples were assayed in duplicate. Optical densities were determined on a CLARIOstar Microplate Reader (BMG LabTech).

Statistical analysis

Analyses were conducted with GraphPad Prism 7.0 software. Data were tested for normality and found to be nonnormally distributed. Accordingly, data are presented as median (interquartile range), Kruskal–Wallis analysis was used to evaluate differences between multiple groups and Dunn's multiple comparison test was used for post-hoc analysis. The diagnose potential of soluble adhesion molecules in anti-NMDAR encephalitis were assessed with the receiving operating characteristic (ROC) curve analysis. Correlation analysis was performed with Spearman analysis. All analyses were two-tailed, and values of $P < 0.05$ were considered statistically significant.

Results

Clinical characteristics

Demographic and clinical characteristics of patient were presented in Table 1. All patients with anti-NMDAR

encephalitis were positive for anti-NMDAR antibody tests in CSF and 21 patients were positive for serum tests, four patients were detected with ovarian teratoma. There were no statistically significant differences on sex or age in each group.

CSF and serum levels of adhesion molecules in patients with anti-NMDAR encephalitis

Median CSF levels of sICAM-1, sVCAM-1, and sL-selectin were all elevated in the anti-NMDAR encephalitis group compared with the SP group (sICAM-1: $P = 0.006$, sVCAM-1: $P = 0.001$, sL-selectin: $P = 0.001$) or NID control group (sICAM-1: $P = 0.001$, sVCAM-1: $P < 0.001$, sL-selectin: $P = 0.003$) (Fig. 1A–C, respectively). Serum levels of sVCAM-1 were also significantly reduced, by approximately a 50%, in the anti-NMDAR encephalitis group (335.69 ng/mL; 225.05–462.78 ng/mL) in comparison with the SP group (218.94 ng/mL; 169.37–313.73 ng/mL; $P = 0.002$) and NID control group (216.43 ng/mL; 208.66–231.47 ng/mL; $P < 0.001$) (Fig. 1E). There were no significant differences in serum levels of sICAM-1 or sL-selectin between the anti-NMDAR encephalitis participants and controls (Fig. 1D and F). Correlation between CSF and serum levels of sICAM-1, sVCAM-1, and sL-selectin levels in anti-NMDAR encephalitis patients were

Table 1. Clinical characteristics of patients.

	Anti-NMDAR encephalitis	SP	NID
Number of patients (<i>n</i>)	26	11	22
Gender (female/male)	14/12	7/4	11/11
Age (years)	33 (17.5–53.25)*	40 (27–53)	38 (23.75–51.75)
Serum albumin (g/L)	38.6 (33.55–41.4)	–	40.55 (37.53–44.33)
CSF albumin (g/L)	0.35 (0.22–0.77)	–	0.34 (0.23–0.45)
Number of symptoms (<i>n</i>)			
Prodrome (headache, fever)	13	0	0
Behavior and cognition disorder	22	0	0
Memory deficit	14	0	0
Speech disorder	15	0	0
Seizures	18	0	0
Movement disorder	11	0	0
Loss of consciousness	15	0	0
Autonomic symptoms	11	0	0
Central hypoventilation	9	0	0
Cerebellar ataxia	0	0	0
Hemiparesis	2	0	0
EEG change	21	0	0
Ovarian teratoma	4	0	0
Onset mRS	4 (3.75–5)	–	–
3 months' mRS	3 (2–3)	–	–
CSF anti-NMDAR antibody	26	0	0
Serum anti-NMDAR antibody	21	0	0

SP, schizophrenia; NID, non-inflammatory disorders.

*Data were presented as the median (interquartile range).

also tested, only sL-selectin showed a positive correlation between CSF and serum levels ($P = 0.001$, $r = 0.595$) (Fig. 2C). In the comparison of patients with anti-NMDAR encephalitis and non-anti-NMDAR encephalitis, the area under the ROC curve (AUC) was 0.981 for CSF sVCAM-1, which was superior to others (CSF sICAM-1: 0.787, CSF sL-selectin: 0.740, serum sICAM-1: 0.516, serum sVCAM-1: 0.801, serum sL-selectin: 0.556), the optimal cut-off values for CSF sVCAM-1 were 5.25 ng/mL. Besides, combination of sICAM, sVCAM, and sL-selectin in CSF and serum did not show an improved diagnose potential for anti-NMDAR encephalitis (Table 2).

Altered CSF levels of adhesion molecules in the follow-up for anti-NMDAR encephalitis patients

We obtained 3-month follow-up CSF and serum samples from nine patients with anti-NMDAR encephalitis and found that the levels of all three adhesion molecules in

CSF and serum were significantly decreased (Fig. 3). The change in CSF sVCAM-1 levels was most pronounced, from (5.08 ng/mL; 3.30–8.96 ng/mL) (onset) to (4.15 ng/mL; 3.09–6.03 ng/mL) (6-month follow-up) ($P = 0.008$), although the latter was still higher than controls ($P < 0.001$).

Associations of adhesion molecules levels with mRS scores and clinical behaviors

We then examined whether there was correlation between the levels of adhesion molecules and neurological condition among patients with anti-NMDAR encephalitis. A significant positive correlation was observed between onset mRS score and the CSF levels of adhesion molecules (sICAM-1: $r = 0.612$; $P = 0.001$, sVCAM-1: $r = 0.498$; $P = 0.01$, sL-selectin: $r = 0.582$; $P = 0.002$) (Fig. 4A–C), serum levels of sVCAM-1 and sL-selectin were also associated with mRS score at disease onset (sVCAM-1: $r = 0.614$; $P = 0.001$, sL-selectin: $r = 0.417$; $P = 0.034$) (Fig. 4D and E). However, only CSF sVCAM-1 levels were found to be

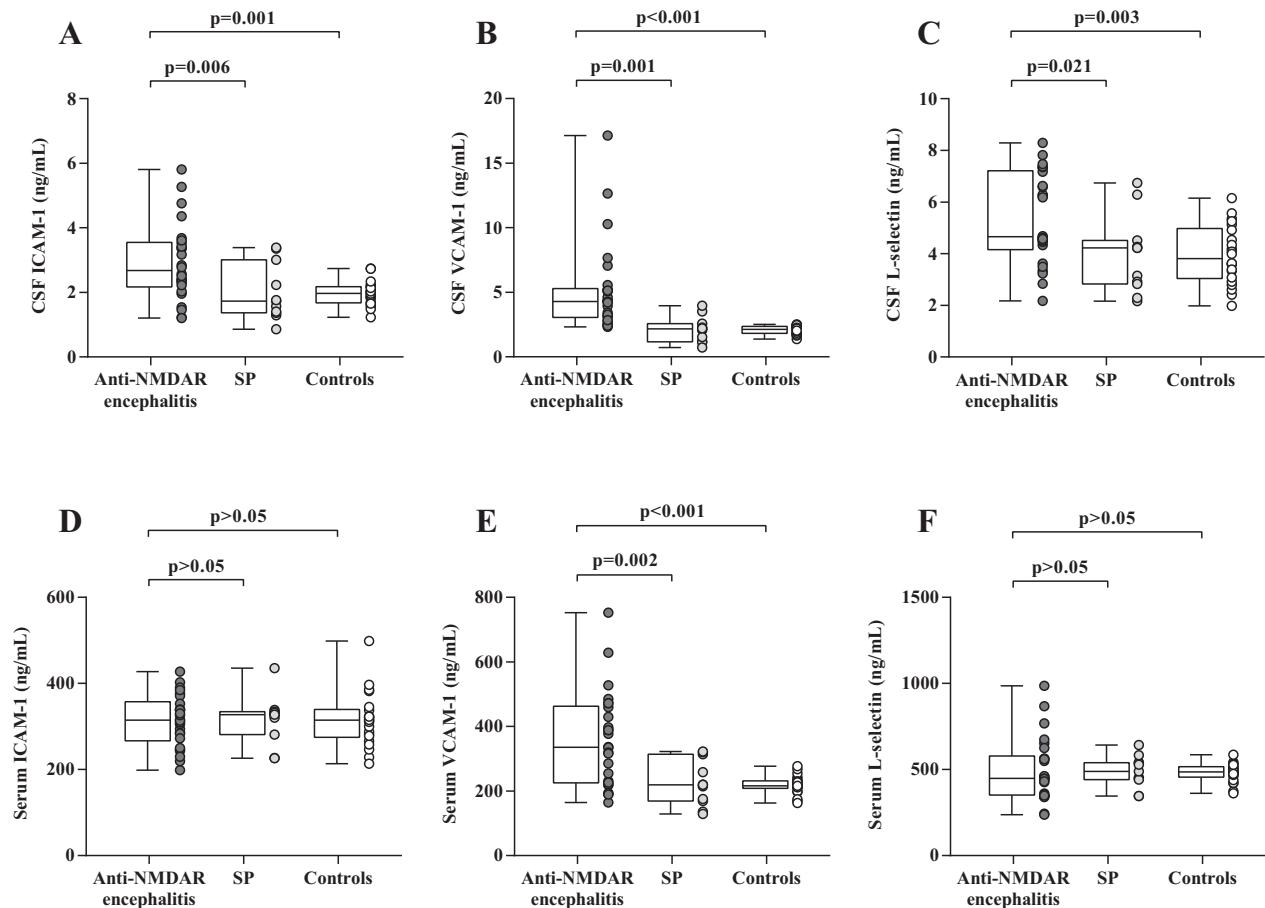


Figure 1. CSF and Serum concentration of sICAM-1, sVCAM-1 and sL-selectin in anti-NMDAR encephalitis, SP and NID patients (A–F).

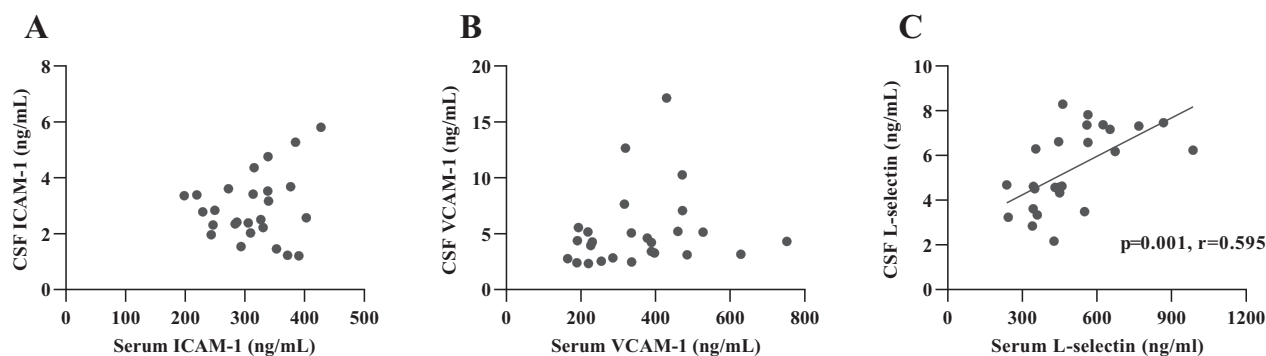


Figure 2. Correlation between CSF and serum levels of sICAM-1, sVCAM-1 and sL-selectin levels in anti-NMDAR encephalitis patients (A–C) (Spearman test).

Table 2. ROC analysis of CSF and serum adhesion molecules.

	AUC	95% CI
Anti-NMDAR encephalitis versus non-Anti-NMDAR encephalitis		
CSF ICAM-1	0.787	0.647–0.926
CSF VCAM-1	0.981	0.951–1.010
CSF L-Selectin	0.740	0.600–0.880
Serum ICAM-1	0.516	0.350–0.682
Serum VCAM-1	0.801	0.669–0.930
Serum L-Selectin	0.556	0.380–0.732
CSF ICAM/serum ICAM	0.774	0.636–0.913
CSF VCAM/serum VCAM	0.719	0.568–0.869
CSF L-Selectin/serum L-Selectin	0.771	0.639–0.903
CSF ICAM-1 + CSF VCAM-1 + CSF L-Selectin	0.960	0.919–1
serum ICAM-1 + serum VCAM-1 + serum L-Selectin	0.902	0.823–0.981
CSF ICAM-1 + serum ICAM-1	0.780	0.649–0.91
CSF VCAM-1 + serum VCAM-1	0.951	0.9–1
CSF L-Selectin + serum L-Selectin	0.767	0.644–0.89

CSF, cerebrospinal fluid; AUC, area under the curve; CI, confidence interval.

correlated with mRS score at 3-month follow-up ($r = 0.439$; $P = 0.025$) (Fig. 4B). Besides, no significant association was found between adhesion molecules and the appearance of specific clinical features, such as prodromal symptoms, cognitive deficits, dyskinesia, and tumor (Table S1).

Discussion

Anti-NMDAR encephalitis is characterized by antibody-mediated autoimmune responses to the CNS, the main symptoms being cognitive impairment and mental psychiatric symptoms, 80% of patients were found with early cerebrospinal fluid abnormalities, mainly characterized by lymphocytosis.^{18,19} Literatures also demonstrate central

nervous system inflammatory infiltration during anti-NMDAR encephalitis, mainly characterized by perivascular lymphocytic infiltration.²⁰

Both circulatory and central systemic inflammation could affect the production and migration of anti-NMDAR antibodies and plasma cells.^{21,22} Studies have found that breakdown of BBB integrity is relevant to the present and severity of neuropsychiatric symptoms caused by anti-NMDAR antibodies.^{23,24} Considering the high seroprevalence of anti-NMDAR antibodies in healthy individuals,²⁴ changes in BBB permeability may be essential for the pathogenesis of anti-NMDAR receptor encephalitis.

The recruitment of circulating leukocytes to target tissues is a critical stage in the inflammatory diseases, it is controlled by multiple steps that mediate initial leukocyte binding, rolling along the surface of the blood vessels, and subsequent adhesion to the target. ICAM-1, VCAM-1, and L-selectin facilitate leukocyte migration across the BBB, which may take part in the pathophysiology of anti-NMDAR encephalitis (Fig. S1).

In this study, anti-NMDAR encephalitis patients showed significantly higher CSF sICAM-1, sVCAM-1, and sL-selectin levels when compared with SP or NID groups, whereas there was no difference regarding serum sICAM-1 and sL-selectin levels. There was a significant association between the CSF levels of all three adhesion molecules and disease severity, but only serum sVCAM-1 levels are associated with disease prognosis.

ICAM-1 is expressed on leukocytes, endothelial cells and upregulated in response to inflammatory signals.²⁵ Although the primary source of sICAM-1 under normal human conditions has not been fully elucidated, the literature indicates that a large source of sICAM-1 is derived from endothelial cells and is elevated in patients with various inflammatory syndromes.^{26,27} Studies have shown that ICAM-1 is involved in the pathogenesis of a

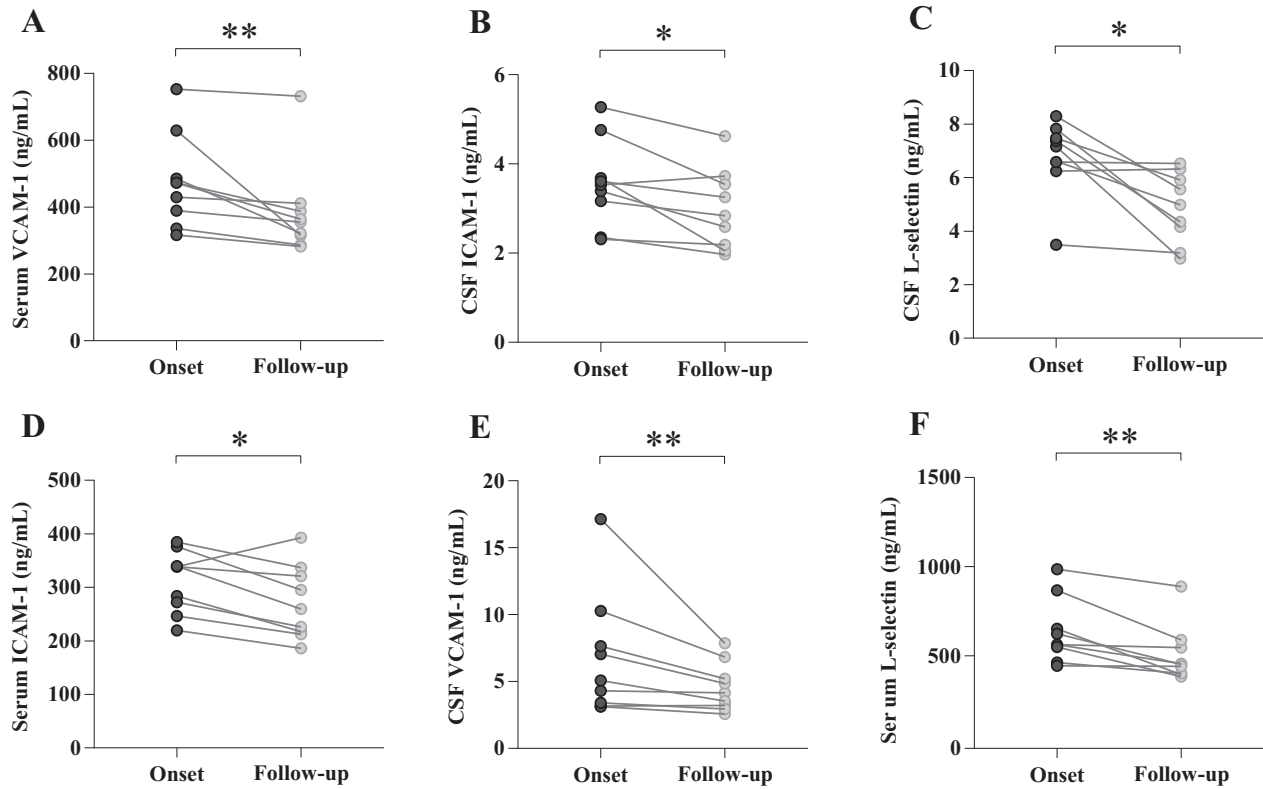


Figure 3. Levels of CSF sICAM-1, sVCAM-1 and sL-selectin in the nine patients with anti-NMDAR encephalitis who received a follow-up test during remission (*P* values: * <0.05; ** <0.01).

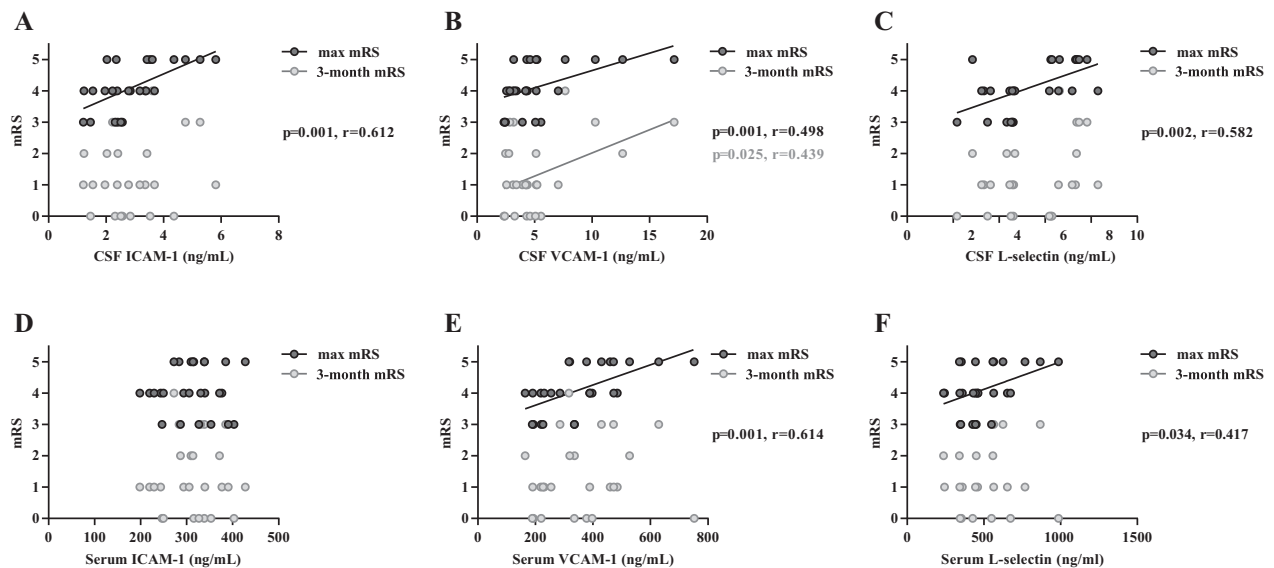


Figure 4. Correlation of CSF and serum levels of sICAM-1, sVCAM-1 and sL-selectin with onset mRS and 3 months' mRS in anti-NMDAR encephalitis patients (A–F) (Spearman test).

variety of autoimmune diseases.^{28,29} In mice model of multiple sclerosis, ICAM-1^{-/-} or mutant mice showed reduced T-cell infiltration in the CNS and lower clinical

grading.³⁰ VCAM-1 is expressed by activated endothelial cells and macrophages,⁷ and the circulating form has been shown critical role to promote monocyte

chemotaxis in responding to inflammatory diseases.^{31–33} In our study, VCAM-1 was found significantly increased in CSF and serum, and associated with mRS both at baseline and 3-month follow-up, initial prodromal symptoms in patients with anti-NMDAR encephalitis may be related to the role of VCAM-1 in inducing leukocyte aggregation and migration. If the patient responds to treatment, the level of VCAM-1 will decrease rapidly, with decreased leukocyte infiltration, and the apoptosis of plasmablast, resulting in a slow decline in antibody titer and recovery. Long-term high expression of VCAM-1 may result in persistent CNS inflammation with severe neurological conditions.

The soluble forms of both VCAM-1 and L-selectin have been reported with chemotactic effects on B cells.^{34,35} The role of B cells in anti-NMDAR encephalitis has been well established, after crossing BBB, the memory B cells would undergo restimulation and maturation into antibody-producing plasma cells,³⁶ VCAM-1 and L-selectin may be involved in maintaining the long-term presence of B cells in the CNS and sustained intrathecal antibody synthesis, which affects the outcome of anti-NMDAR encephalitis.

Evidence suggested a link between adhesion molecules and cognitive impairment,^{37,38} however, it was not found in patients with anti-NMDAR encephalitis, probably due to differences in the mechanisms that lead to cognitive function changes in anti-NMDAR encephalitis, mainly by antibody-mediated changes in neuronal function. The expression of adhesion factors in SP patients differed from varied reports,^{39,40} our results found no significant difference when comparing with other noninflammatory CNS diseases, but due to the small number of samples, caution should be exercised when interpreting these results.

Since early treatment is closely linked to the prognosis of anti-NMDAR encephalitis, sensitive biomarkers would be particularly useful.⁴¹ In our study, sVCAM-1 levels in CSF correlate with mRS scores both at onset and 3-month follow-up, suggesting a high level of sVCAM-1 may indicate severe clinical outcomes and poor prognosis for NMDAR encephalitis. Thus, changes in CSF sVCAM-1 combined with anti-NMDAR antibody titers may be promising indicators for predicting anti-NMDAR encephalitis.

Conclusion

Although the etiopathology of anti-NMDAR encephalitis remains unclear, there are increasing evidences that dysfunction in the immune system involved in this disease. Data for this study showed that adhesion molecules, sICAM-1, sVCAM-1, and sL-selectin are elevated in patients with anti-NMDAR encephalitis. These elevated

levels were associated with high mRS score, and could act as an indicator for the severity and prognosis of anti-NMDAR encephalitis, further investigations aimed at determining the interaction between immune cells and behavior in patients with anti-NMDAR encephalitis are needed.

Ethics Statement

The study protocol was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University, each participant provided written informed consent to participate.

Acknowledgments

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Author Contributions

H. W., W. X. and S. P. conceived this study and designed the experiments. Y. D., C. Y., Z. Z., Y. P., J. C., H. X., Y. C. and K. O. collected the samples and clinical data. YD and CY performed the experiments and analyzed the data. Y. D., H. W. and W. X. wrote the manuscript. All authors read and approved the final manuscript and agreed to submit it for publication.

Conflict of Interest

All authors read and approved the final manuscript. They declare no conflicts of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. ICAM-1, VCAM-1, and L-selectin and their ligands at leucocytes and CNS endothelial cells.

Table S1. Correlation between clinical manifestations and the level of adhesion factors in anti-NMDAR encephalitis patients.