European Review for Medical and Pharmacological Sciences 2023; 27: 9721-9728

Relationship of immune cells with disability and cognitive impairment in patients with neuromyelitis optica spectrum disorder

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Abstract. – OBJECTIVE: This study aimed to investigate the relationship between common clinical immune indicators, disability degree, and cognitive impairment in patients with neuromyelitis optica spectrum disorder (NMOSD).

PATIENTS AND METHODS: We retrospectively analyzed lymphocyte subsets and routine parameters in the peripheral blood of 55 patients with NMOSD. We assessed the degree of disability using the Extended Disability Status Scale (EDSS). The Montreal Cognitive Assessment (MoCA) scores were used to assess cognitive function. In addition, we also determined the cytokine levels in 33 patients with NMOSD. The relationships of these immunological indicators with disability and cognitive impairment were assessed using correlation and multiple linear regression analyses.

RESULTS: The results of the multiple linear regression analysis suggested that for patients with NMOSD, the neutrophil-lymphocyte ratio (NLR) (β=0.072, *p*=0.034) and number of attacks (β=0.131, *p*=0.03) were positively correlated with EDSS scores, whereas the number of attacks was positively correlated with MoCA scores. In addition, we also collected cytokine levels in 33 of these patients. The results of the study showed a positive correlation between IL-10 and EDSS scores and a negative correlation between IL-6 and MoCA scores.

CONCLUSIONS: Our results show that these immune cells and cytokines are, to some extent, associated with the degree of disability and cognitive impairment in patients with NMOSD. Closely monitoring these indicators may allow detecting changes in patients' disease courses and predicting the severity of their disease. In clinical practice, this may facilitate early intervention and appropriate treatment decisions, which may improve the management of patient prognosis.

Key Words:
Neuromyelitis optica spectrum disorder, Lymphocyte, Cytokine, Disability, Cognitive impairment.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a recurrent central nervous system (CNS) autoimmune disease characterized by demyelination, inflammatory cell infiltration, and axonal loss. This disorder can impact the brain, spinal cord, and optic nerve, and multiple episodes can result in severe neurological dysfunction, which can significantly reduce the quality of life for patients. In recent years, studies[1] have revealed that patients with NMOSD can also suffer from varying degrees of cognitive impairment, primarily affecting their memory function, attention, and executive function, thereby further adding to their burden.

NMOSD is characterized by humoral immune-mediated inflammation of the CNS, and it is associated with a crucial role played by aquaporin-4-immunoglobulin G (AQP4-IgG), which is produced by B cells and binds to Aquaporin-4 (AQP4) receptors in astrocytes[2]. This bind initiates complement activation and causes inflammatory cell infiltration, astrocyte damage, demyelination, and nerve loss[3]. Multiple immune cells and cytokines are involved in this process by mediating adaptive and intrinsic immune responses[4]. AQP4-IgG titer changes in the cerebrospinal fluid are closely related to disease activity[5]; however, many studies[6-9] have shown that these serum titers do not accurately reflect the severity, activity, or prognosis of the disease. Compared to cerebrospinal fluid tests, blood tests are noninvasive, convenient, and easy to perform in clinical practice; Therefore, it is essential to identify blood indicators that influence the degree and progression of disability in patients with NMOSD, allowing for better monitoring.

In the present study, we collected data on immunological indicators and measured the Extended

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Disability Status Scale (EDSS) and the Montreal Cognitive Assessment (MoCA) scores in patients with NMOSD after an acute attack. We then analyzed the relationship of immune cells and cytokines with disability and cognitive impairment in these patients. Our study focused on the usefulness of these commonly used immunological indicators in clinical settings for monitoring disease progression and identifying potential treatments.

Patients and Methods

Participants

We retrospectively enrolled 55 patients with NMOSD in the acute phase admitted to the Department of Neurology of Shanxi Medical University First Hospital between January 2020 and November 2022. The inclusion criteria were: (1) patients meet the 2015 NMOSD diagnostic criteria[10], (2) an acute attack is defined as the presence of new objective neurological signs lasting for at least 24 hours, (3) patients have not been treated with any immunotherapy before the blood collection, and (4) the EDSS score and MoCA scores were determined by an experienced clinician on the first day of admission. The exclusion criteria were: (1) missing blood test results, and (2) another concurrent autoimmune disease, digestive system disease, cardiovascular disease, malignant tumor, etc. This study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University (Ethics number: 2020-K-K056). Informed consent was obtained from all participants.

Data Collection

General data included sex, age, disease duration, number of attacks, recurrence rate, and EDSS score. Based on the disease duration and number of attacks, the annual recurrence rate (ARR) was calculated. Patients' cognitive function was assessed using the MoCA score. The following laboratory parameters were included in the analysis: (1) lymphocyte subsets, including the percentages and counts of lymphocytes, T lymphocytes, $CD4^+$ T lymphocytes, $CD8^+$ T lymphocytes, B lymphocytes, and natural killer (NK) cells; (2) routine blood parameters, including absolute neutrophil count (ANC), absolute monocyte count (AMC), absolute lymphocyte count (ALC), and the neutrophil-lymphocyte ratio (NLR), as well as the lymphocyte-monocyte ratio (LMR), were calculated; and (3) levels of cytokines, including interleukin (IL)-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF)-α and interferon (IFN)-γ.

Statistical Analysis

SPSS 26.0 statistical software (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. The Kolmogorov-Smirnov test was used to analyze whether the data were normally distributed. Data are presented as mean and standard deviation for data that follow a normal distribution, or as median and interquartile range for data that do not follow a normal distribution. For correlation analyses, the Pearson correlation was used for normally distributed data and the Spearman correlation for all other data types. Factors with a significant difference ($p<0.05$) in the correlation analysis were included in the stepwise multiple linear regression analysis.

Results

General Clinical Characteristics

According to the inclusion and exclusion criteria, 55 patients with NMOSD were finally included in the study. The NMOSD group included 40 women and 15 men with an average age of 45.42±16.68 years. Their average EDSS score was 4.24±1.33, and the average MoCA score was 23.45±3.78 ($p<0.05$; Table I).

Correlation of Clinical Characteristics, Lymphocyte Subsets, and Blood Cell Counts with EDSS and MoCA Scores in NMOSD Patients

To clarify the correlation of clinical characteristics and immune cells with EDSS and MoCA scores in patients with NMOSD, we performed a correlation analysis. In patients with NMOSD, EDSS scores were positively correlated with the number of attacks ($p=0.003$), ANC ($p=0.043$), and NLR ($p=0.002$), and negatively correlated with $CD8^+$ T cell count ($p=0.050$) and ALC. MoCA scores were positively correlated with the number of attacks ($p=0.0049$; Table II).

Significant parameters in the correlation analysis were further tested in multiple linear regression analyses performed in a stepwise fashion after normalization. According to the results, NLR ($\beta=0.072$, $p=0.034$) and number of attacks ($\beta=0.131$, $p=0.03$) were positively correlated with EDSS score (Figure 1A-B). Since the correlation analysis showed that the MoCA score was only associated with the number of attacks (Figure 1C), the multiple regression analysis was not performed further.

Correlation of Cytokine Levels with EDSS and MoCA Scores in NMOSD Patients

In addition to immune cells, cytokines play an essential role in the development and progression of MS and NMOSD. Thus, we also determined the levels of cytokines, including IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, and IL-17A in 33 patients with NMOSD. We then performed correlation and regression analyses. The correlation analysis showed that IL-10 levels exhibited a significant correlation with EDSS scores, whereas negative correlations of IL-6 levels with MoCA scores were found in patients with NMOSD (Table III, Figure 1D-E). For the remaining cytokines, the correlation was not significant.

Table I. Characteristics of all patients in the NMOSD group.

	NMOSD
General clinical characteristics	
Sex	15/40
Age	45.42±16.68
Disease duration	3 (1, 10)
Number of attacks	3 (2, 5)
ARR	1 (0.55, 1)
EDSS score	4.24±1.33
MoCA score	23.45±3.78
Lymphocyte percentage (%)	
Total lymphocyte	18.26 (10.42, 22.70)
Total T lymphocyte	76.20±12.07
$CD4^+$Tcell	42.30±9.93
$CD8^+$T cell	29.7±9.89
B cell	9.87 (5.10, 13.60)
NK cell	8.52±6.24
Lymphocyte count (/ul)	
Total lymphocyte	1,739.22±824.41
Total T lymphocyte	1,358.24±677.24
$CD4^+$Tcell	699 (481, 1,005)
$CD8^+$T cell	429 (291, 669)
B cell	135 (56, 252)
NK cell	112 (62, 191)
CD4:CD8	1.47 (1.07, 1.88)
Blood cell count	
ANC ($*10^9$/L)	3.9 (2.8, 6.3)
ALC ($*10^9$/L)	1.74±0.78
AMC ($*10^9$/L)	0.49±0.25
NLR	1.96 (1.43, 4.16)
LMR	3.50 (2.50, 4.75)

ARR, the annual recurrence rate; EDSS, the Extended Disability Status Scale; MoCA, the Montreal Cognitive Assessment; NK, natural killer; ANC, absolute neutrophil count; AMC, absolute monocyte count; ALC, absolute lymphocyte count; NLR, the neutrophil-lymphocyte ratio; LMR, the lymphocyte-monocyte ratio.

Discussion

NMOSD is an inflammatory disease of the CNS characterized by autoimmune-mediated demyelination and neurodegeneration. Despite the low incidence of NMOSD in China[11,12], it can result in different degrees of physical disability and cognitive impairment, which negatively affect the patient's quality of life. Accordingly, it is crucial to investigate factors that influence the disability in patients with NMOSD. This can help improve the quality of life and prognosis of patients with NMOSD, as well as guide clinicians to manage the disease better.

NMOSD is considered a humoral immune-mediated inflammation of the CNS, with AQP4-IgG playing a key role. AQP4-IgG titer changes in the cerebrospinal fluid are closely related to disease activity[5]; however, many studies[6-9] have shown that these serum titers do not accurately reflect the severity, activity, or prognosis of the disease. Compared to cerebrospinal fluid tests, blood tests are noninvasive, convenient, and easy to perform in clinical practice; therefore, finding blood indicators that affect the degree and progression of disability in patients with NMOSD is essential to identify changes in the condition of these patients.

In our study, neutrophils and NLR were positively correlated with disability in NMOSD patients, and T lymphocytes and $CD8^+$ T lymphocytes were negatively correlated with disability in NMOSD patients. Further linear regression results showed that NLR was independently associated with the degree of disability in patients. Various studies[13,14] have found increased NLRs in patients with NMOSD in acute phases. Neutrophils are an important part of the NLR. It was also shown that damaged astrocytes can secrete pro-inflammatory cytokines that stimulate neutrophil production in the bone marrow[15], and these neutrophils can migrate to the CNS in the action of chemokines to fully activate and cause injury. This may explain why patients with NMOSD have a greater degree of neutrophil infiltration than patients with MS[16]. Thus, neutrophils may be involved in the pathogenesis of NMOSD. Additionally, lymphocyte numbers represent the numerator of the NLR, with T and B lymphocytes being equally important. It has been shown in mice that damage appears only in the presence of both AQP4-IgG and T cells[17]; however, another study[18] in rats demonstrated that AQP4-IgG can induce NMOSD pathology without the assistance of T cells. In clinical studies[19], patients receiving immunotherapy showed significant increases in total T lymphocyte percentage and $CD8^+$ T lym-

Table II. Correlation of clinical characteristics, lymphocyte subsets, and blood cell counts with EDSS and MoCA scores in the NMOSD group.

	EDSS score		MoCA score	
	r	*p*	r	*p*
Characteristic				
Sex	0.020[b]	0.883	-0.095[b]	0.492
Age	0.056[a]	0.684	-0.028[a]	0.837
Disease duration	0.203[b]	0.137	-0.218[b]	0.11
number of attacks	0.388[b]	0.003*	-0.267[b]	0.049*
ARR	-0.064[b]	0.641	0.043[b]	0.757
Lymphocyte percentage (%)				
Total lymphocyte	-0.233[b]	0.087	0.007[b]	0.957
Total T lymphocyte	-0.198[a]	0.148	-0.067[a]	0.628
$CD4^+$Tcell	-0.095[a]	0.488	0.108[a]	0.432
$CD8^+$T cell	-0.095[a]	0.490	-0.116[a]	0.397
B cell	0.032[b]	0.816	-0.003[b]	0.98
NK cell	0.090[a]	0.515	-0.015[a]	0.911
Lymphocyte count (/ul)				
Total lymphocyte	-0.200[a]	0.144	0.127[a]	0.356
Total T lymphocyte	-0.213[a]	0.118	0.064[a]	0.642
$CD4^+$Tcell	-0.159[b]	0.247	0.037[b]	0.788
$CD8^+$T cell	-0.266[b]	0.050*	0.051[b]	0.712
B cell	0.050[b]	0.718	0.160[b]	0.245
NK cell	-0.161[b]	0.242	0.081[b]	0.554
CD4:CD8	0.026[b]	0.850	0.073[b]	0.598
Blood cell count				
ANC (*10^9/L)	0.274[b]	0.043*	0.091[b]	0.509
ALC (*10^9/L)	-0.289[a]	0.032*	0.077[a]	0.576
AMC (*10^9/L)	-0.070[a]	0.61	0.209[a]	0.125
NLR	0.400[b]	0.002*	0.025[b]	0.858
LMR	-0.074[b]	0.597	-0.133[b]	0.344

*p<0.05; **p<0.01; [a]the r value of the Pearson correlation; [b]the r value of the Spearman correlation. ARR, the annual recurrence rate; EDSS, the Extended Disability Status Scale; MoCA, the Montreal Cognitive Assessment; NK, natural killer; ANC, absolute neutrophil count; AMC, absolute monocyte count; ALC, absolute lymphocyte count; NLR, the neutrophil-lymphocyte ratio; LMR, the lymphocyte-monocyte ratio.

Table III. Correlation of cytokine levels with EDSS and MoCA scores in the NMOSD group.

	EDSS score		MoCA score	
	r	*p*	r	*p*
IL-2	0.003[b]	0.988	-0.227[b]	0.204
IL-4	0.007[b]	0.968	-0.289[b]	0.103
IL-6	0.317[b]	0.072	-0.389[b]	0.025*
IL-10	0.381[b]	0.029*	-0.054[b]	0.767
TNF-α	-0.030[b]	0.867	-0.260[b]	0.144
IFN-γ	0.056[b]	0.757	-0.325[b]	0.065
IL-17A	-0.126[b]	0.486	-0.262[b]	0.141

*p<0.05; **p<0.01; [a]the r value of the Pearson correlation; [b]the r value of the Spearman correlation. TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ.

phocyte percentage, and further analysis of $CD8^+$ T lymphocyte subsets showed that immunotherapy was correlated with an increase in naïve $CD8^+$ T cells and a decrease in effector/memory $CD8^+$ T cells. In summary, although we found that T lymphocytes and $CD8^+$ lymphocytes were negatively correlated with the degree of disability in patients, there is some controversy concerning the role of T cells in NMOSD, and a larger sample size is needed to explore this phenomenon further.

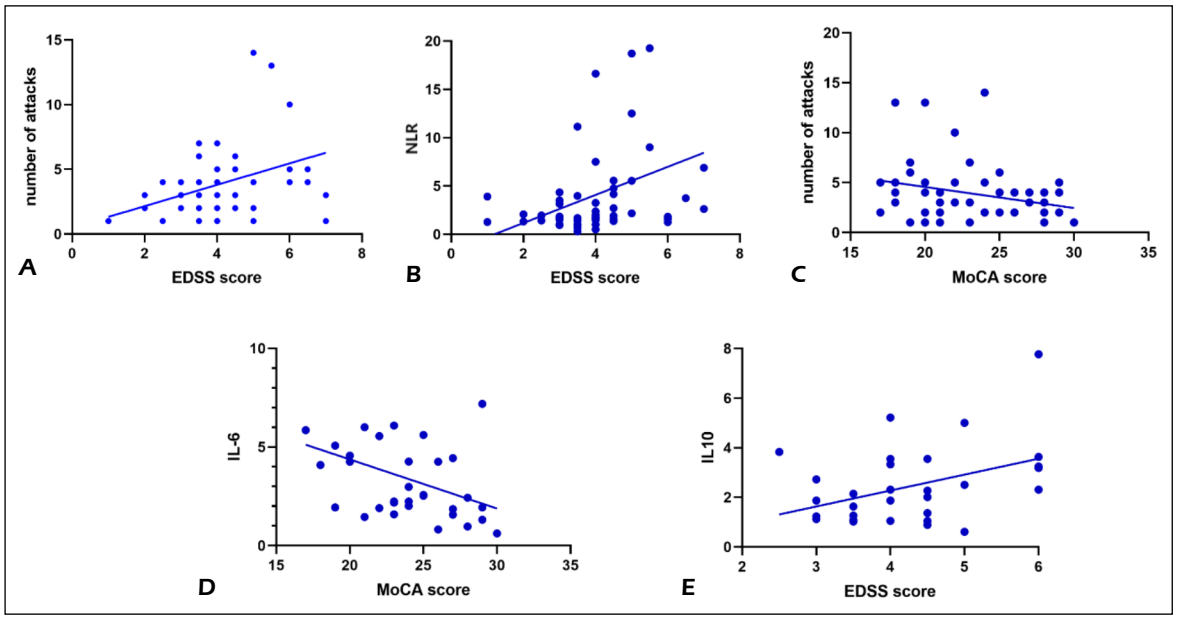

Figure 1. Correlation of immune cells with EDSS and MoCA score in patients with NMOSD. **A**, correlation of number of attacks with EDSS score; (**B**) correlation of NLR with EDSS score; (**C**) correlation of number of attacks with MoCA score; (**D**) correlation of IL-6 with MoCA score; (**E**) correlation of IL-10 with EDSS score.

Compared to ANC and ALC, NLR is a combination of two markers and is less susceptible to interference by other factors, therefore reflecting the inflammatory status of the body more accurately. In clinical studies[20], a significant correlation has been found between NLR and the prognosis of NMOSD patients, with those who had a high NLR showing poorer recovery. NLR is also an independent risk factor for neurological impairment in patients experiencing the first attack[21]. However, the contribution of NLR in patients with relapsing NMOSD is unclear. Our study, which included patients with varying numbers of attacks, showed that NLR was independently and positively associated with disability. NLR measurements are simple, economical, and easily obtained. This parameter can be used to monitor changes in the patient's condition and to assess the prognosis of patients with NMOSD.

In addition, our study found that in NMOSD patients, the number of attacks was positively correlated with the degree of disability and cognitive function. Neurological dysfunction in patients with NMOSD generally accumulates during acute attacks over time. As the number of relapses increases, nerve cells and neurotransmission pathways sustain more damage, leading to more dysfunction and disability. In clinical studies[22,23], the progression of disability and cognitive impairment in patients were closely related to the number of attacks. Our results support these findings, highlighting the importance of timely treatment and relapse prevention for NMOSD patients. Therefore, managing relapses is crucial to minimizing the impact of NMOSD on patients' quality of life.

To further assess immune cell function, we also tested serum cytokine levels in NMOSD patients. According to our results, IL-10 was positively correlated with EDSS scores in NMOSD patients. It was observed that IL-10 levels improve symptoms in MS patients and mice, but its role in NMOSD is unclear. Wang et al[24] found that IL-10 levels were elevated in patients with NMOSD and were predictive of NMOSD development. Similarly, high levels of IL-10 were found to be associated with morbidity in patients with systemic lupus erythematosus and blocking IL-10 improved disease outcomes[25]. These findings may be related to the role of IL-10 in promoting the proliferation of B cells and the production of antibodies[26]. Our study found a relationship between EDSS scores and IL-10 in NMOSD patients, but further studies are needed to confirm this. In addition, we found that IL-6 was negatively correlated with cognitive function in NMOSD patients. IL-6 may play various roles in NMOSD pathogenesis, including the promotion

of plasmablast survival, stimulation of AQP4-IgG production, disruption of the integrity and function of the blood-brain barrier, and enhanced differentiation and activation of pro-inflammatory T lymphocytes[27]. While normal levels of IL-6 can support cognitive function during neuroinflammation by enhancing the survival of newborn neurons, overexpression of IL-6 can impair cognitive function by disrupting the structure and function of the blood-brain barrier[28,29]. Our study's findings are consistent with previous literature. In summary, our study supports the applicability of these cytokines as effective indicators for clinical evaluation and provides new directions for the investigation of pathogenesis and therapeutic targets.

Limitations

The limitations of this study are as follows: (1) This study had a relatively small sample size, which may have influenced the results. (2) As the study was designed to investigate common clinical indicators of hospitalization, the subsets of $CD4^+$ T cells, $CD8^+$ T cells, and B cells were not further classified. (3) Since this was a cross-sectional study, we were not able to monitor each indicator longitudinally. Consequently, it is necessary to further confirm the findings of this study by undertaking a longitudinal study with a larger sample size.

Conclusions

This study investigated the effects of immune cells and cytokines on the degree of disability and cognitive impairment in patients with NMOSD. Our results show that peripheral blood parameters are correlated with disability and cognitive impairment in a disease-specific manner that may have prognostic value. Close monitoring of these indicators in clinical practice may support the observation of changes in the condition of patients and the selection of treatment options. These findings may improve the management of patients with NMOSD.

Ethics Approval

This study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University (approval number: 2020-K-K056).

Informed Consent

Informed consent was obtained from all participants. The patients and their families understood the research content and methods.

Funding

The study is supported by The Applied Basic Research Plan of Shanxi Province (201901D211487).

Authors' Contributions

Conceptualization, Meini Zhang and Yuanyuan Zhang; Data curation, Jiayang Li, Li Wang and Ying Wang; Formal analysis, Jiayang Li; Investigation, Jiayang Li, Li Wang and Ying Wang; Methodology, Jiayang Li; Project administration, Jiayang Li and Huiru Xue; Resources, Huiru Xue and Meini Zhang; Software, Jiayang Li; Supervision, Huiru Xue; Visualization, Jiayang Li; Writing – original draft, Jiayang Li; Writing – review and editing, Jiayang Li, Huiru Xue, Meini Zhang and Yuanyuan Zhang.

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Data Availability

The data used to support the findings of this study are included in the article.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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