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ORIGINAL RESEARCH

The Percentage of Neutrophils is Independently Associated with Blood-Brain Barrier(BBB) Disruption in Myelin Oligodendrocyte Glycoprotein Antibody Associated Disease (MOGAD)

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Purpose: This study aims to investigate the risk factors associated with blood-brain barrier(BBB) disruption in patients with myelin oligodendrocyte glycoprotein antibody associated disease(MOGAD).

Patients and Methods: We collected clinical data from 95 patients diagnosed with MOGAD at the Department of Neurology, the First Affiliated Hospital of Zhengzhou University from October 2018 to May 2024. Patients were classified into normal or damaged BBB groups based on cerebrospinal fluid (CSF) albumin/serum albumin (QAlb). Binary logistic regression analysis was used to evaluate the risk factors for BBB disruption in MOGAD patients.

Results: Our study revealed that in MOGAD patients with BBB damaged, there is a higher proportion of acute phase high EDSS scores, higher incidence of prodromal symptoms, and a higher rate of viral infections. Myelitis is the main clinical phenotype, with clinical manifestations primarily including limb weakness and bladder/bowel dysfunction. Laboratory tests showed higher levels of CSF protein, immunoglobulin (IgG), 24-hour intrathecal IgG synthesis rate, peripheral blood leukocytes, neutrophil percentage, NLR, anti-thyroglobulin antibodies(TGAbs), and fibrinogen levels, while free triiodothyronine (FT3) and lymphocyte percentage were lower. Multivariate regression analysis indicated that an increased neutrophil percentage is an independent risk factor for BBB damage in MOGAD patients (OR=1.068, 95% CI: 1.018–1.122, P=0.008).

Conclusion: Neutrophil percentage is a readily available and widely used indicator reflecting the immune system's state and the body's inflammation level. The change in neutrophil percentage is independently associated with BBB damage in MOGAD patients. This finding helps provide more reference information for personalized treatment decisions and further research into the pathogenesis of MOGAD.

Keywords: myelin oligodendrocyte glycoprotein antibody associated disease, blood-brain barrier, central nervous system, the percentage of neutrophils, clinical characteristics, treatment, responsiveness, viral infections

Introduction

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an immune-mediated, acquired inflammatory demyelinating disease of the central nervous system (CNS). MOGAD can present as a monophasic or relapsing course, with no significant differences in gender or racial prevalence. The clinical manifestations are diverse and complex, including meningoencephalitis, optic neuritis, myelitis, and brainstem encephalitis. Although the clinical phenotypes and imaging features of MOGAD overlap with other CNS inflammatory demyelinating diseases, the immune injury mechanisms and histopathological changes are distinct. MOGAD is currently recognized as a clinical entity

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separate from multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD).Myelin oligodendrocyte glycoprotein (MOG) is a transmembrane protein exclusively expressed on the surface of mature oligodendrocyte membranes. The presence of MOG-IgG in serum is a key biomarker for diagnosing MOGAD. Similar to aquaporin-4 (AQP4) antibodies, MOG-IgG predominantly belongs to the IgG1 subtype. IgG1 antibodies are produced by peripheral plasma cells, indicating that the primary source of MOG antibodies in the central nervous system is the periphery.[1–3] These antibodies, along with immune cells, cross the compromised blood-brain barrier (BBB)—which can be disrupted by activated T cells, infections, or immune responses—entering the perivascular space and the CNS, ultimately leading to disease.[4] Clearly, BBB plays a crucial role in the pathogenesis of MOGAD.

BBB plays a central role in maintaining homeostasis within the CNS. This barrier not only prevents the entry of pathogenic and harmful substances but also regulates immune responses. When BBB permeability increases, peripheral inflammatory mediators, immune cells, and viruses can infiltrate the CNS, leading to disease. It has been reported that neuroinflammation is associated with BBB dysfunction in diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), stroke, and MS.[5] Moreover, some studies suggest that elevated BBB permeability is linked to the development of psychiatric disorders, such as depression.[6] These findings indicate that evaluating BBB function could be beneficial for clinical research on neurological diseases.

Neutrophils are an important component of the immune system, primarily involved in inflammation and immune regulation by secreting cytokines, chemokines, and reactive oxygen species (ROS). Recent studies have demonstrated that neutrophils play a crucial role in various neurological diseases, particularly in the disruption of the BBB and the worsening of stroke prognosis. Specifically, neutrophil infiltration is considered a significant factor in the destruction of the blood-brain barrier, which further influences the pathological progression of stroke. In one animal study, researchers used neutrophil-depleting neutralizing antibodies in a focal cerebral ischemia mouse model, and found that this intervention significantly reduced BBB disruption, as well as alleviated brain injury and inflammation[7] In addition to stroke, recent studies have also emphasized the role of neutrophils in the pathogenesis of MS. Neutrophils contribute to BBB disruption through the production of myeloperoxidase (MPO), ROS, and the pro-inflammatory cytokine IL-1β.[8] These findings indicate that neutrophils play a crucial role in maintaining the integrity of the blood-brain barrier in stroke and multiple sclerosis. However, to date, similar studies have not been conducted in MOGAD. Therefore, investigating the role of neutrophils in MOGAD, particularly their impact on BBB integrity, may provide new insights into the pathogenesis of the disease and offer potential therapeutic targets for clinical intervention.

Currently, the BBB is believed to be involved in the pathogenesis of CNS demyelinating diseases, including MS, NMOSD, and MOGAD.[9–11] Although the detailed mechanisms of BBB dysfunction in these diseases remain unclear, research indicates that AQP4 and MOG antibodies do not directly impact BBB function, suggesting that other factors contribute to the disruption of BBB integrity.[12,13] However, no studies have yet examined the risk factors associated with BBB damage in MOGAD patients.

The permeability of the BBB can be assessed by comparing cerebrospinal fluid (CSF) albumin/serum albumin (QAlb) or by using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). QAlb is a quantitative index based on the concentration of albumin in cerebrospinal fluid and serum, represented as the ratio of cerebrospinal fluid albumin to serum albumin (QAlb = AlbCSF/AlbSerum).[14] It directly reflects BBB permeability and is characterized by high sensitivity and simplicity. As such, it is better suited for quantitatively assessing global, long-term, or subtle changes in BBB permeability. In contrast, enhanced MRI lacks a direct quantitative index and cannot precisely measure BBB permeability, making it challenging to detect mild, global changes. Therefore, in this study, we chose QAlb to evaluate BBB integrity.Recent studies have shown that the clinical characteristics and treatment responsiveness of various autoimmune-related diseases, such as NMOSD, MS, and autoimmune encephalitis(AE), are associated with QAlb.[15–18] However, the relationship between BBB integrity and clinical features or immune treatment responsiveness in MOGAD patients remains unclear and requires further investigation.

Therefore, we retrospectively analyzed the clinical data and laboratory results of MOGAD patients diagnosed at the Department of Neurology, First Affiliated Hospital of Zhengzhou University. We compared the clinical characteristics, immune treatment responsiveness, and other differences between the group with normal BBB integrity and the group with BBB impairment. Additionally, we analyzed the relevant risk factors influencing BBB permeability. This study aims to provide more reference data for personalized treatment decisions and further research into the pathogenesis of MOGAD.

Materials and Methods

Study Design and Population

We retrospectively collected clinical data from 95 MOGAD patients diagnosed in the Department of Neurology at the First Affiliated Hospital of Zhengzhou University between October 2018 and May 2024. The inclusion criteria for the study subjects were as follows: (1) Meeting the diagnostic criteria from the "Chinese Expert Consensus on the Diagnosis and Treatment of Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease", including: ① Serum MOG-IgG positivity detected using a cell-based assay with full-length human MOG as the target antigen; ② Clinical presentation with one or a combination of the following: a. Optic neuritis (ON), including chronic relapsing inflammatory optic neuropathy; b. Transverse myelitis (TM); c. Encephalitis or meningoencephalitis; d. Brainstem encephalitis; ③ MRI or electrophysiological findings (visual evoked potentials for isolated ON patients) associated with CNS demyelination; ④ Exclusion of other diagnoses; (2) Positive detection of MOG antibodies in cerebrospinal fluid (CSF) and/or serum (antibody testing outsourced to KingMed Diagnostics); (3) Acute phase onset and treatment with first-line immunotherapy only. Exclusion criteria were: (1) Non-first onset of MOGAD; (2) Presence of other CNS demyelinating disease antibodies that preclude clear identification of the responsible antibody (eg anti-glial fibrillary acidic protein (GFAP) antibodies, anti-aquaporin protein-4 (AQP4) antibodies); (3) Prior immunotherapy before hospital admission; (4) History of diseases that severely affect motor ability and visual function (eg trauma and acute cerebrovascular disease); (5) Incomplete clinical data.

The specific diagnostic criteria were as follows: If a patient had one of the core clinical attack types and the presence of serum MOG-IgG was confirmed as positive by fixed-cell or live-cell CBA, a diagnosis of MOGAD could be made. For patients presenting with one of the core clinical attack types of MOGAD, the diagnosis could still be made only when at least one supportive clinical or MRI feature was present under the following circumstances: ①Serum MOG-IgG results were weakly positive at a low titer by fixed-cell or live-cell CBA. ②Serum MOG-IgG was positive by fixed-cell CBA but without a defined titer. ③Serum MOG-IgG was negative, but the CSF test results were clearly positive.

Data Collection and Definitions

Based on electronic medical record systems, We retrospectively collected clinical and laboratory data from electronic medical records of enrolled patients, including: demographic information (gender and age), prodromal symptoms (fever, cough, diarrhea, etc)., clinical manifestations (eye pain, visual impairment, seizures, headache, altered consciousness, psychiatric abnormalities, cognitive impairment, dizziness, cranial nerve involvement, limb weakness, sensory disturbances, urinary and fecal incontinence), presence of viral infection, ICU admission, coexistence of other positive antibodies, and treatment regimens. Additional examinations included: ① Peripheral blood cell count and percentages within 24 hours of admission (white blood cells, neutrophils, lymphocytes, monocytes), Neutrophil-to-lymphocyte ratio (NLR), Monocyte-to-lymphocyte ratio (MLR), thyroid function (thyroid stimulating hormone TSH, free triiodothyronine FT3, free thyroxine FT4), thyroid-related antibodies (anti-thyroid peroxidase antibody TPOAb, anti-thyroglobulin antibody TGAb, thyroid stimulating hormone receptor antibody TSHR-Ab), and fibrinogen. ② 3T MRI imaging examination: ③ Cerebrospinal fluid (CSF) examination: Elevated pressure defined as >180mmH_2O, elevated protein level defined as >450mg/L, elevated glucose level defined as >4.5mmol/L, elevated chloride level defined as >130mmol/L, elevated immunoglobulin IgG defined as >40mg/L, and 24-hour intrathecal IgG synthesis rate indicating intrathecal synthesis occurrence, calculated as: [(IgGCSF-IgGSerum/369)- (AlbCSF-AlbSerum/230) x (IgGSerum/AlbSerum)x0.43] x5,[19] with a reference range for 24-hour intrathecal IgG synthesis rate of −9.9 to 3.3 (mg/dl), >3.3 (mg/dl) indicating intrathecal synthesis; IgG index calculated as (IgGCSF/IgGSeru)/(AlbCSF/AlbSerum),[20] IgG index >0.70 indicating intrathecal IgG synthesis; QAlb was the ratio of CSF albumin to serum albumin (QAlb=AlbCSF/AlbSerum).[14] All statistical results were obtained prior to immunotherapy. Due to the age dependency of QAlb,[21] the normal value of QAlb for each patient is calculated as QAlb*=(4+age/15)x10^{-3}.[14] Due to ethical and clinical constraints, this study did not include a healthy control group. In this study, patients were grouped based on the QAlb value from the first CSF examination after hospital admission. Patients with QAlb>QAlb* were classified as having BBB damage, referred to as the BBB damaged group, while those with QAlb≤QAlb* were classified as the BBB normal group.

Assessment of Disease Severity

We evaluated disease severity using the EDSS scale upon admission and after 30 days of initial immunotherapy in our study. The EDSS scale encompasses eight functional systems of the CNS: pyramidal function, cerebellar function, brainstem, sensory function, bowel and bladder function, visual function, cerebral function, and other functions, with scores ranging from 0 to 10. Disease severity assessments at all stages were independently conducted by two neurologists unaware of the patients' diagnoses, through retrospective analysis of medical records provided for this study.

Treatment Protocols and Assessment of Immunotherapy Responsiveness

Treatment methods were standardized first-line immunotherapies, including methylprednisolone pulse therapy (initial dose of 1000 mg/day intravenous infusion, tapered by half every 3 days until reaching 60 mg/day orally for maintenance), intravenous immunoglobulin (2g/kg, administered over 3–5 days), and plasma exchange (every other day, for a total of 5 cycles). The attending physician determined the patient's immunotherapy regimen based on clinical symptoms, treatment response, and drug safety considerations. Typically, methylprednisolone pulse therapy was preferred. In cases of contraindications such as advanced age, allergies, diabetes mellitus, or severe gastrointestinal ulcers, intravenous immunoglobulin or plasma exchange was selected. Combination therapies were considered if a single treatment modality was ineffective. Typically, methylprednisolone combined with plasma exchange was chosen; methylprednisolone combined with intravenous immunoglobulin was chosen in cases of hemodynamic instability, severe infection, difficulty obtaining blood products, or heparin allergy. A minority of patients received triple therapy. Good immunotherapy responsiveness is defined as an EDSS score lower than the admission score after 30 days of first-line immunotherapy, while poor responsiveness is defined as no change or higher scores.

Statistical Analysis

All data were statistically analyzed using SPSS version 26.0 (IBM, Chicago, IL, USA). Continuous variables conforming to a normal distribution were presented as mean ± standard deviation (x±s), and intergroup comparisons were conducted using independent samples *t*-test. Non-normally distributed continuous variables were defined as median and interquartile range (M, IQR) and compared by Mann–Whitney *U*-test between two groups. Categorical data were presented as counts (percentages), and intergroup comparisons were analyzed using the chi-square test or Fisher's exact test. Risk factor analysis was conducted using both univariate and multivariate logistic regression analysis. The ability of neutrophil percentage to predict BBB damage was evaluated using receiver operating characteristic (ROC) curves, with the area under the curve (AUC) calculated, and the level of significance was defined as $P < 0.05$.

Results

Comparison of Clinical Characteristics

Of the 95 MOGAD patients, 59 (62.1%) were included in the normal BBB group, and 36 (37.9%) were included in the BBB damaged group. Compared to the normal BBB group, patients in the BBB damaged group had a higher severity rate of symptoms at onset (EDSS score > 3), a higher incidence of prodromal symptoms, and a higher rate of viral infections. The clinical phenotype was primarily myelitis, with predominant clinical manifestations of limb weakness and bowel and bladder dysfunction, and these differences were statistically significant ($P < 0.05$). Additionally, there were no statistically significant differences between the two groups in the incidence of clinical phenotypes such as brainstem encephalitis, meningoencephalitis, and optic neuritis, nor in gender, age at onset, presence of anti-nuclear antibodies, or the rate of other positive autoimmune antibodies ($P > 0.05$)(Table 1).

In terms of auxiliary examinations, the BBB damaged group had higher proportions of elevated CSF protein levels, IgG, and 24-hour intrathecal IgG synthesis rate compared to the normal BBB group, with statistically significant differences ($P < 0.05$). There were no statistically significant differences between the two groups in CSF pressure, glucose levels, chloride levels, or IgG index ($P > 0.05$).

In peripheral blood tests, the BBB damaged group showed higher white blood cell count, percentage of neutrophils, NLR value, anti-thyroglobulin antibody levels, and fibrinogen levels compared to the normal BBB group. Conversely, the

Table 1 The Demographic and Clinical Characteristics Between Normal BBB and Damaged BBB Groups

Variables	Total (n=95)	BBB Normal Group (n=59)	BBB Damaged Group (n=36)	P Value
Gender, n (%)				
Male	54(56.8%)	33(55.9%)	21(58.3%)	0.819
Female	41(43.2%)	26(44.1%)	15(41.7%)	
Age (years)	21(8.5–29.0)	25.92(11.00–44.00)	18.44(13.00–22.00)	0.753
High EDSS score at onset (EDSS>3) n (%)	56(59.8%)	30(50.8%)	26(72.2%)	**0.040***
Prodromal symptoms, n (%)	31(32.6%)	14(23.7%)	17(47.2%)	**0.018***
Clinical phenotype, n (%)				
Optic neuritis	33(34.7%)	22(37.3%)	11(30.0%)	0.504
Meningoencephalitis	50(52.6%)	30(50.8%)	20(55.6%)	0.656
Brainstem encephalitis	14(14.7%)	9(15.3%)	5(13.9%)	0.855
Myelitis	35(36.8%)	17(28.8%)	18(50.0%)	**0.038***
Clinical manifestations, n (%)				
Seizures	24(25.3%)	13(22.0%)	11(30.6%)	0.354
Headache	20(21.1%)	11(18.6%)	9(25.0%)	0.461
Cognitive impairment	4(4.2%)	4(6.8%)	0(0%)	0.285
Consciousness impairment	5(5.3%)	3(5.1%)	2(5.6%)	1.000
Psychobehavioral disturbances	3(3.2%)	2(3.4%)	1(2.8%)	1.000
Eye pain	16(16.8%)	12(20.3%)	4(11.1%)	0.244
Vision loss	30(30.5%)	20(33.9%)	10(27.8%)	0.534
Dizziness	5(5.3%)	3(5.1%)	2(5.6%)	1.000
Cranial nerve involvement	12(13.2%)	8(14.0%)	4(11.8%)	1.000
Limb weakness	30(31.6%)	14(23.7%)	16(44.4%)	**0.035***
Sensory impairment	17(17.9%)	9(15.3%)	8(22.2%)	0.390
Bowel and bladder dysfunction	12(12.6%)	3(5.1%)	9(25.0%)	**0.012***
Viral infections, n (%)	23(24.2%)	9(15.3%)	14(38.9%)	**0.009***
ICU admission, n (%)	27(28.4%)	15(25.4%)	12(33.3%)	0.407
Anti-nuclear antibodies, n (%)	44(46.3%)	24(40.7%)	20(55.6%)	0.158
Other positive autoimmune antibodies, n (%)	10(10.5%)	8(13.6%)	2(5.6%)	0.218

Notes: Data are shown as mean ± SD, median [range] or n (%). Significant values ($P < 0.05$) are highlighted in bold.
Abbreviations: BBB, blood-brain barrier; ICU, intensive care unit.

percentage of lymphocytes and FT3 levels were lower in the BBB damaged group, with these differences being statistically significant ($P < 0.05$). Other blood parameters did not show statistically significant differences. Additionally, there were no statistically significant differences between the two groups in the rate of MRI abnormalities (Table 2).

Table 2 Comparison of the Ancillary Examinations Between Normal BBB and Damaged Groups

Variables	Total (n=95)	BBB Normal Group (n=59)	BBB Damaged Group (n=36)	P Value
White blood cell count (×109 /L)	8.70(6.73–12.85)	7.42(6.87–10.29)	9.70(6.75–14.70)	**0.016***
Neutrophil percentage (%)	69.88(62.11–78.37)	62.75(56.70–66.57)	78.22(60.73–81.40)	**0.001***
Lymphocyte percentage (%)	22.00(13.40–28.49)	26.06(17.81–31.68)	15.70(11.70–29.75)	**0.044***
Monocyte percentage (%)	5.82(4.38–7.28)	7.43(6.02–8.01)	5.96(5.02–7.94)	0.098
NLR value	3.23(2.20–5.90)	2.44(1.96–4.24)	5.10(2.04–6.87)	**0.020***
MLR value	0.25(0.19–0.40)	0.25(0.17–0.42)	0.32(0.22–0.49)	0.243
TPOAB (×IU/mL)	9.73(9.00–16.95)	9.02(9.00–14.40)	17.20(9.00–65.70)	0.387
TGAB (×IU/mL)	13.46(10.70–19.18)	12.55(10.18–14.08)	19.30(13.35–214.50)	**0.019***
TRAB (×IU/L)	0.80(0.80–0.83)	0.80(0.71–0.81)	0.80(0.80–0.99)	0.280

(*Continued*)

Table 2 (Continued).

Variables	Total (n=95)	BBB Normal Group (n=59)	BBB Damaged Group (n=36)	P Value
FT4 (×pmol/L)	13.10(10.63–15.32)	11.67(10.63–13.72)	13.50(9.55–15.38)	0.152
FT3 (×pmol/L)	4.86(4.26–5.41)	4.89(4.11–5.65)	4.69(4.25–5.04)	**0.018***
TSH (×μIU/mL)	1.69(0.72–2.66)	2.47(1.28–3.03)	2.40(1.32–4.56)	0.881
Fibrinogen (×g/L)	3.24±0.93	3.08±0.98	3.51±0.85	**0.037***
CSF routine, n (%)				
Increased CSF pressure (>180 mmH_2O)	34(35.8%)	18(30.5%)	16(44.4%)	0.169
Increased CSF protein (>450 mg/L)	16(16.8%)	2(3.4%)	14(38.9%)	**<0.001***
Increased CSF glucose (>4.5 mmol/L)	9(9.5%)	7(11.9%)	2(5.6%)	0.511
Increased CSF chloride (>130mmol/L)	8(8.4%)	4(6.8%)	4(11.1%)	0.472
CSF electrophoresis, n (%)				
Increased CSF immunoglobulin IgG (>40mg/L)	37(38.9%)	10(16.9%)	27(75%)	**<0.001***
Increased IgG index (>0.7)	47(49.5%)	27(45.8%)	20(55.6%)	0.354
Increased 24 h intrathecal IgG synthesis rate (>3.3 mg/24 h)	37(38.9%)	16(27.1%)	21(58.3%)	**0.002***
Abnormal MRI, n (%)	87(91.6%)	54(91.5%)	33(91.7%)	1.000

Notes: Data are shown as media [range] or n (%) values. Significant values (P < 0.05) are highlighted in bold.
Abbreviations: BBB, blood-brain barrier; CSF, cerebral spinal fluid; MRI, magnetic resonance imaging; NLR, neutrophils/lymphocytes ratio; MLR, monocytes/lymphocytes ratio; TGAB, thyroglobulin antibodies; TPOAB, thyroid peroxidase antibody; FT4, free thyroxine; FT3, free Triiodothyronine; TSH, thyroid stimulating hormone; TRAB, thyroid stimulating hormone receptor antibodies.

Comparison of Treatment Response

Of the 95 MOGAD patients undergoing treatment, 61 patients received methylprednisolone pulse therapy alone, 2 patients received intravenous immunoglobulin (IVIG) alone, 29 patients received a combination of methylprednisolone and IVIG, 1 received methylprednisolone pulse therapy combined with plasma exchange, and 2 patients received a combination of methylprednisolone pulse therapy, plasma exchange and IVIG. None of the patients received second-line immunotherapy or other immunotherapies within the first 30 days of initial immunotherapy.

The severity of the patients' conditions was assessed using the Expanded Disability Status Scale (EDSS) at the time of admission and 30 days after the initial immunotherapy. The differences in EDSS scores before and after treatment were analyzed to compare the response to immunotherapy between the two groups. After 30 days of initial immunotherapy, 79 patients (83.2%) showed improvement compared to their condition at admission, while 16 patients (16.8%) either worsened or showed no change. The rate of good response to immunotherapy was lower in the BBB damage group compared to the normal BBB group (P < 0.05)(Table 3).

Analysis of Risk Factors Associated with BBB Damage in MOGAD Patients

To identify the risk factors associated with BBB damaged in MOGAD patients, we performed a univariate logistic regression analysis. The results showed that the presence of prodromal symptoms, viral infections, fibrinogen levels, and neutrophil percentage were associated with BBB damage in MOGAD patients. Further multivariate logistic regression

Table 3 Comparison of Treatment Response Between Normal BBB Group and Damaged BBB Group

	Total (n=95)	BBB Normal Group (n=59)	BBB Damaged Group (n=36)	P Value
EDSS score better, n (%)	79(83.2%)	53(89.8%)	26(72.2%)	**0.026***
EDSS score worse, n (%)	16(16.8%)	6(10.2%)	10(27.8%)	

Notes: Data are shown as media [range] or n (%) values.Significant values (P < 0.05) are highlighted in bold.

Table 4 Univariate and Multivariate Analyses on Factors Affecting the Integrity of BBB by Logistic Regression Models

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Prodromal symptoms (%)	2.876(1.184–6.987)	**0.020***	2.145(0.747–6.162)	0.156
Viral infections (%)	3.535(1.332–9.383)	**0.011***	3.148(0.949–10.441)	0.061
Neutrophil percentage (%)	1.070(1.027–1.116)	**0.001***	1.068(1.018–1.122)	**0.008***
Fibrinogen (×g/L)	1.645(1.020–2.653)	**0.041***	1.150(0.656–2.018)	0.625

Notes: Significant values (P < 0.05) are highlighted in bold.

analysis indicated that, after adjusting for prodromal symptoms, viral infections, and fibrinogen levels, the neutrophil percentage was found to be an independent risk factor for BBB damaged in MOGAD patients (OR = 1.068, 95% CI: 1.018–1.122, P = 0.008), with statistically significant differences. The detailed results were shown in the Table 4.

OR = 1.068 represented the odds ratio, which indicated that for each 1% increased in the neutrophil percentage, the relative odds of blood-brain barrier disruption increased by 6.8%. Although the OR value was small, it still highlighted the potential role of neutrophils in BBB disruption. Therefore, future studies would need to increase the sample size to further explore the relationship. And we conducted the Hosmer-Lemeshow test to evaluate the model's goodness of fit. The test yielded a chi-square value of 6.031 with a p-value of 0.644, which was greater than 0.05, indicating that the model fits the data well.

We used the receiver operating characteristic (ROC) curve to evaluate the predictive efficacy of this risk factor for BBB damaged in MOGAD patients. According to the ROC curve, the optimal cutoff value for neutrophil percentage to predict BBB damaged in MOGAD patients was 77.86%, with a sensitivity of 52.8% and a specificity of 86.2%. The area under the curve (AUC) was 0.713 (95% CI: 0.604–0.823, P = 0.001), indicating a moderate predictive efficacy. The details were shown in the Figure 1.

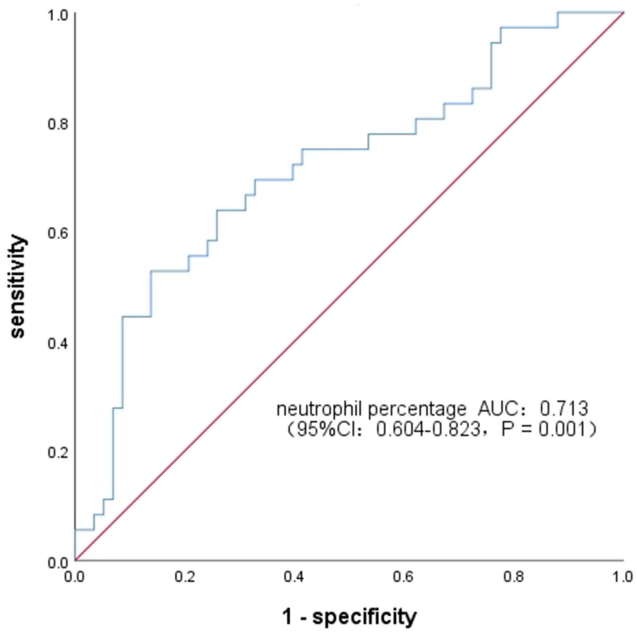

Figure 1 ROC curve analysis of the predictive value of neutrophil percentage for BBB damage in MOGAD patients.
Abbreviations: ROC, receiver operating characteristic; BBB, blood-brain barrier.

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The neutrophil percentage has moderate predictive performance as a marker for BBB disruption in MOGAD patients, with high specificity but low sensitivity. This suggests that it performs well in excluding patients without BBB disruption, but has certain limitations in identifying those with BBB disruption. Therefore, future studies could further explore integrated assessment models combining additional clinical indicators and biomarkers to improve predictive efficacy.

Discussion

Group-Specific Variations in Clinical Measures

In this study, we retrospectively analyzed the relationship between BBB integrity and clinical and laboratory indicators in 95 MOGAD patients. Under normal conditions, the albumin content in CSF is extremely low, mainly derived from plasma through the ultrafiltration function of the BBB. Albumin is neither synthesized nor metabolized within the nervous system. When the BBB is disrupted, albumin can easily enter the CSF from the blood due to the significant concentration gradient, leading to changes in the composition of the CSF.[22] Currently, Qalb is commonly used to assess BBB integrity and has been shown to correlate with age.[21] Previous studies have indicated a correlation between BBB integrity and disease severity. A retrospective study on NMOSD patients revealed that Qalb is associated with the severity of the initial attack and the length of spinal cord lesions, suggesting that it could serve as a biomarker for predicting the severity and clinical features of NMOSD.[23] Marzena et al, using a mouse model of multiple sclerosis, evaluated BBB permeability by detecting the entry of the marker sodium fluorescein into spinal cord tissue and found a positive correlation between BBB permeability and clinical scores on the day of sampling.[24] Collectively, these findings support the results of our study. In a multicenter study involving 50 anti-MOG antibody-positive patients, it was found that approximately 13.3% of patients with an optic neuritis clinical phenotype had BBB damage, while the proportion increased to 47.6% in patients with myelitis and/or encephalitis, brainstem encephalitis.[25,26] In our study, BBB impairment was predominantly observed in patients with a clinical phenotype of myelitis, which is consistent with previous reports.

Viral infections are closely related to demyelinating diseases of the CNS. A Mendelian randomization study suggests a potential causal relationship between infections with herpes simplex virus and varicella-zoster virus and the onset of NMOSD.[27] Epstein-Barr virus (EBV) has increasingly been recognized as an important factor in the pathogenesis of MS. The risk of developing MS is significantly increased following EBV infection, which is associated with high levels of EBV-specific antibodies in the host.[28] Previous studies have also reported phenotypes of optic neuritis and encephalomyelitis with positive anti-MOG antibodies following infections with EBV and genital herpes simplex virus.[29–31] Since the outbreak of the COVID-19 pandemic, several case studies have reported COVID-19 infection preceding the onset of MOGAD,[32,33] with a median time from COVID-19 diagnosis to MOGAD onset of 6 days (range: −7 to 45 days). Clearly, there is a close relationship between prodromal viral infections and the onset of MOGAD, although the specific pathogenesis remains unclear. Our study results indicate that the rate of viral infections in the BBB damaged group of MOGAD patients is higher than that in the intact BBB group. According to current literature, the possible mechanism is that viral infections can affect the functional homeostasis of the BBB, alter its permeability, and induce pro-inflammatory and anti-inflammatory immune responses within the BBB. Many neurotropic viruses can cross the BBB via the bloodstream and eventually invade the CNS.[34] Additionally, a few cases of MOGAD have been reported to occur after vaccination, including influenza, measles/rubella, diphtheria/tetanus/pertussis, and COVID-19 vaccines.[35–38]

Thyroid hormones, including thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3), play crucial roles in regulating neuronal differentiation, migration, and synaptic plasticity, as well as in modulating glial cell function and immune responses in the brain.[39–41] The processes of myelination and remyelination in the CNS also depend on thyroid hormones.[42] An in vitro study by Ben et al demonstrated that T3 promotes the formation of myelinating oligodendrocytes by stimulating oligodendrocyte progenitor cells (OPCs) to cease proliferation and commence differentiation.[43,44] The observed reduction in CNS myelination in hypothyroid patients and rodents confirms the necessity of T3 for oligodendrocyte formation, development, and myelination.[45] A case-control study on MOGAD indicated that patients with low T3 syndrome had higher EDSS scores and a higher proportion of adverse outcomes, suggesting that low T3 syndrome is associated with increased severity during acute exacerbations of MOGAD.[46] Low T3 syndrome is frequently observed in various autoimmune diseases, such as systemic lupus erythematosus, MS, and

NMOSD.[47] Furthermore, previous studies have shown that abnormal thyroid antibodies are associated with the degree of disability in NMOSD patients.[48] The related mechanism might involve multiple autoantibody binding sites on thyroglobulin (TG) and thyroid peroxidase (TPO), which cross-react with myelin-associated antigens or through molecular mimicry.[49] Anti-thyroid antibodies can form immune complexes with myelin basic protein (MBP) and induce demyelination.[50] Inflammation in demyelinating diseases of the CNS is often associated with BBB disruption. Our study results indicate that FT3 levels were lower and anti-thyroglobulin antibody levels were higher in the BBB damaged group compared to the normal BBB group. Considering the mechanisms mentioned above, we propose that thyroid function and antibody abnormalities indicate an autoimmune state. Infections and inflammatory factors can further exacerbate immune dysregulation, leading to a vicious cycle that results in BBB disruption.[51]

Fibrinogen is a protein synthesized by hepatocytes and circulates in the blood. Although fibrinogen is undetectable in the healthy CNS, it can accumulate significantly in various neurological diseases and traumatic injuries. This accumulation is associated with damage to the BBB. Consequently, fibrinogen has been widely used as a reliable marker for BBB disruption in human tissues and relevant animal models.[52] In this study, fibrinogen levels in the BBB damaged group were higher than those in the BBB normal group, consistent with previous research. After BBB disruption, fibrinogen enters the neural tissue, where it is converted into insoluble fibrin by perivascular tissue factors and abundant procoagulant proteins.[53,54] At the site of BBB disruption, fibrinogen is converted into pro-inflammatory fibrin, which induces the release of reactive oxygen species (ROS) and the activation of M1-type microglia and macrophages.[55,56] The M1-like activation of innate immune cells and ROS damage oligodendrocyte precursor cells (OPCs), potentially hindering myelin regeneration and promoting disease progression.[57,58]

CSF protein and IgG are critical biochemical markers for assessing CNS immune responses.[59] Under physiological conditions, the concentration of proteins and immunoglobulins in cerebrospinal fluid is extremely low. However, when BBB permeability increases, serum immunoglobulins can diffuse into the CNS due to the steep concentration gradient between serum and CSF.[60,61] In this study, the levels of protein and immunoglobulins in the CSF of the BBB damaged group were higher than those in the BBB intact group, consistent with previous studies. However, similar to AQP4-IgG-positive NMOSD, MOG-IgG primarily originates from the peripheral blood but can also be produced intrathecally.[1–3] The intrathecal synthesis rate was higher in the BBB damaged group compared to the BBB intact group, likely due to the influx of peripheral pro-inflammatory T cells and specific B cells through the damaged BBB into the CNS, where they aggregate at inflammation sites and directly secrete specific IgG.[62]

In this study, patients primarily received standard first-line immunotherapy, with some subsequently undergoing second-line treatments. Based on the EDSS scores before and after treatment, the efficacy rate of immunotherapy was lower in the BBB damage group compared to the BBB intact group. We speculate that the possible reason for this is that during BBB damage, peripheral inflammatory mediators and immune cells enter the CNS, exacerbating inflammation and immune responses, which leads to a poor short-term prognosis. A study on AE[18] also supports these findings, indicating that patients with BBB damaged generally have a poorer prognosis and that combination first-line immunotherapy is superior to monotherapy. However, research on different treatment methods and outcomes for MOGAD patients still requires further elucidation.

Increased Neutrophil Percentage as an Independent Risk Factor for BBB Damage

Lymphocytes play a crucial role in the pathogenesis of MOGAD. MOG-IgG is an IgG1 subclass secreted by B cells that possesses complement-activating properties. Follicular T helper cells (Tfh) are essential for the differentiation of MOG-specific B cell subsets.[63] Additionally, CD4+ T cells are the primary inflammatory cell type involved in lesion formation, playing a significant role in disrupting the BBB and creating a pro-inflammatory environment.[64,65] In our study, we observed that the proportion of peripheral blood lymphocytes in the BBB damaged group was lower than that in the BBB intact group. This finding has not been previously reported in MOGAD research. A retrospective study involving 46 NMOSD patients found that the lymphocyte proportion in the BBB damaged group was lower than in the BBB normal group, consistent with our results. This suggests that BBB disruption is associated with peripheral blood lymphocyte imbalance. Based on these findings, we hypothesize that reduced lymphocytes are related to the disruption of immune

homeostasis. In MOGAD, BBB disruption exacerbates inflammatory responses, causes immune dysfunction, and leads to the release of pro-inflammatory cytokines and complement factors, further resulting in leukocyte infiltration.[66]

The neutrophil-to-lymphocyte ratio (NLR) is a biomarker reflecting systemic inflammation extracted from routine blood tests. Historically, NLR has been associated with cancer: a meta-analysis from Canada demonstrated that higher NLR levels in cancer patients are often linked to a poorer prognosis.[67] Recently, NLR has been used to evaluate central nervous system diseases. For instance, a study including 121 cases of Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis showed that severe patients had significantly higher NLR levels compared to mild patients, with high NLR being an independent risk factor for severe cases.[68] In a study of 483 adult MS patients, NLR could differentiate between relapsing-remitting and primary progressive multiple sclerosis and predict disability progression.[69] In NMOSD, NLR is higher than in healthy controls and is significantly associated with relapse and poor prognosis.[70,71] In MOGAD, the NLR in patients with relapses is higher than in healthy controls but lower than in NMOSD patients.[72] In this study, the NLR value in the BBB damaged group was higher than in the BBB normal group, suggesting that BBB integrity is related to systemic inflammatory responses and abnormal immune reactions. Combined with the aforementioned studies, we hypothesize that elevated NLR is associated with an increased risk of relapse and poor prognosis in CNS diseases through inflammatory-induced BBB damage. The underlying mechanisms warrant further investigation.

Neutrophils are the most abundant type of white blood cells and play a pivotal role in the immune response, performing functions such as chemotaxis, phagocytosis, and killing. These cells are recruited to infection sites to help clear extracellular pathogens.[73] In peripheral blood, cytokines and chemokines released by circulating effector cells, such as T cells and neutrophils, are also thought to influence the homeostasis of the CNS barrier. Degranulation of neutrophils may activate the fibrinolytic system, leading to damage to BBB.[74] A study measuring active MMP-9 in the CSF and serum of MS patients found that elevated MMP-9 levels were associated with disease activity.[75] Neutrophils expressing MMP-9 have been found to cause severe degradation of basal layer type IV collagen and blood extravasation, promoting BBB breakdown and neuroinflammation.[76–78] Post-mortem tissue from a MS patient who relapsed after discontinuation of natalizumab treatment revealed a significant presence of neutrophils in the BBB leakage areas.[79] This suggests that neutrophils are involved in the disruption of the BBB in demyelinating neuroinflammatory diseases. A study conducted in China, using an experimental autoimmune encephalomyelitis (EAE) model, demonstrated that the number of neutrophils in the peripheral blood of treatment-naive MS patients positively correlated with BBB permeability. Further investigation revealed that neutrophils promote demyelination through the release of neutrophil extracellular traps (NETs) and secretion of tumor necrosis factor alpha (TNF-α). Additionally, inhibiting neutrophil infiltration through intraperitoneal injections of inhibitors significantly reduced disease scores and demyelination in the EAE model.[8] In addition to this, neutrophils are involved in the breakdown of tight junctions and basement membrane proteins, further contributing to BBB disruption. Neutrophils are the most active cells during the acute phase of stroke. Under the influence of cytokines, they migrate into the brain parenchyma and stimulate the release of ROS. The production of ROS can increase BBB permeability. During ischemic stroke, neutrophils degranulate and release MMP-9, a process that increases BBB permeability. Neumann et al demonstrated that neutrophil infiltration is associated with local BBB damage, and acute inhibition of neutrophil infiltration into the brain may be a valuable therapeutic approach for stroke treatment.[80]

A current neutrophil-centered dual-response delivery system utilizes the intrinsic ability of neutrophils to navigate the BBB.[81] Specifically, when neutrophils respond to infection and inflammatory signals and cross the BBB, they simultaneously deliver the drugs encapsulated within them to accurately target the site of infection. NETs are network-like structures released by neutrophils. Digestion of NETs with DNase1 significantly reduces BBB damage, along with increased coverage of microvascular pericytes and the formation of new functional blood vessels, which improves patient prognosis.[82] In an Alzheimer's disease model, injecting 300 μg of anti-Ly6G antibody every other day for 1 month can selectively deplete neutrophils, leading to improvements in the cognitive function of mice.[83] These findings suggest that the interaction between neutrophils and the BBB has significant potential for the treatment of central nervous system diseases.

Compared to MS, there is relatively less research on the role of neutrophils in MOGAD. A study on MOGAD patients suggested that the percentage of neutrophils is the simplest and most useful marker for distinguishing between MOGAD attacks and remission.[84] Whether these changes in neutrophil percentage are related to alterations in BBB permeability during MOGAD attacks and remission remains to be further investigated.

Limitations

There were several limitations in our study. First, it was a retrospective study; therefore, it was difficult to control for confounding factors. Second, this study was conducted at a single center, which may have led to unintentional bias. Although this study provides preliminary insights into the role of neutrophils in BBB disruption in MOGAD, the lack of a healthy control group due to ethical and clinical limitations means that the results need to be validated in future studies with the inclusion of a control group.This study requires prospective, large-sample, multicenter research to confirm our conclusions.

Conclusion

Our study indicates that the group with BBB damaged exhibits distinct clinical characteristics compared to the BBB normal group, and the BBB damaged group shows a poorer response to immunotherapy. We found that the percentage of neutrophils can be used to predict the integrity of the BBB, providing a basis for implementing personalized treatment in clinical practice and further elucidating the mechanisms of BBB damaged in MOGAD patients.

Data Sharing Statement

All relevant data supporting the findings of this study are available upon request from the corresponding author (Please contact neurologycx@163.com).

Ethics Statement

The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2023-KY-1277-002). The research was conducted after obtaining approval from the ethics committee. This study is a retrospective study, and the data used were obtained from publicly available case records or de-identified patient information, making it impossible to obtain individual patient consent. An exemption from obtaining informed consent has been granted. This study strictly followed ethical review procedures and was approved by the relevant ethics committee, ensuring that all patient privacy and personal information were fully protected. The study does not involve any direct intervention or disclosure of patient privacy.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors report no conflicts of interest in this work.

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