

# Effect of Low Complement C4 on Clinical Characteristics of Patients with First-Episode Neuromyelitis Optica Spectrum Disorder

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**Purpose:** To describe and compare the clinical features of patients with first-episode neuromyelitis optica spectrum disorder (NMOSD) in a normal complement C4 group and a low complement C4 group, and explore the mechanism by which low complement C4 affects the clinical features of patients with NMOSD.

**Patients and Methods:** We retrospectively analyzed clinical data of 169 aquaporin-4 (AQP4) antibody positive patients with NMOSD from the First Affiliated Hospital of Zhengzhou University from December 2013 to March 2021. Prior to treatment, the blood was drawn for detection, and the patients underwent a 3.0 Tesla MRI examination. A low complement C4 level was defined as a serum complement C4 level  $<0.14$  g/L. Depending on whether the complement C4 level was reduced, it was divided into the normal complement C4 group and low complement C4 group. The basic demographics, clinical manifestations, laboratory examinations, and imaging findings of the two groups were compared.

**Results:** Among the 169 AQP4 antibody positive patients, 54 were low-complement C4 patients and 115 were normal. There were no significant differences in the demographics, clinical manifestations, treatment options, or admission Expanded Disability Status Scale (EDSS) score between two groups ( $P > 0.05$ ). The median of discharged EDSS was the same (4 vs 4), but the difference between the two was statistically significant ( $P = 0.019$ ). Compared with the normal complement C4 group, the blood uric acid level (225 vs 179;  $P = 0.001$ ) and the C3 level (1.06 vs 0.87,  $P = 0.000$ ) of the low complement C4 group were significantly lower. The incidence of brainstem lesions in patients with low complement C4 was higher (53.7% vs 33%,  $P = 0.01$ ).

**Conclusion:** The treatment effect of the first-episode AQP4 antibody positive NMOSD low complement C4 group was poor, the blood-brain barrier was more severely damaged, and the disease changes were likely to involve the brainstem.

**Keywords:** blood-brain barrier, brainstem, humoral immunity, optic neuritis

## Introduction

Neuromyelitis optica spectrum disease (NMOSD) is an inflammatory demyelinating disease of the central nervous system, which is mediated by humoral immunity, most commonly affecting the optic nerve and spinal cord.<sup>1,2</sup> The clinical manifestations of NMOSD are mostly optic neuritis and long-segment transverse myelitis. It is generally believed that the aquaporin-4 (AQP-4) antibody is the specific disease marker of NMOSD.<sup>1-4</sup> B cells are the main participants in humoral immunity, and the AQP4-IgG antibody produced after activation into plasma cells binds to the AQP-4 antigen on the surface of astrocytes, ultimately leading to central

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demyelination and neuronal degeneration.<sup>5</sup> In this process, complement-dependent cytotoxicity and classical complement activation pathways are key parts of the pathogenesis of NMOSD.<sup>6–8</sup> Studies have shown that the levels of complement C3 and C4 in patients with NMOSD are lower than those in healthy individuals.<sup>9</sup> In clinical practice, we found that the levels of complement C4 in some patients with NMOSD was not abnormal. Thus, in this study, we aimed to assess the effects of complement C4 on the clinical characteristics of patients with NMOSD and to determine possible underlying mechanisms to help inform diagnosis and treatment.

## Materials and Methods

### Study Design and Population

This is a retrospective, observational, single-center study in which we analyzed the clinical data of patients with newly diagnosed NMOSD at the First Affiliated Hospital of Zhengzhou University from December 2013 to March 2021. The inclusion criteria were as follows: (1) first-episode patients; (2) a complete complement test; (3) AQP4 antibody positive patients; (4) without systemic lupus erythematosus (SLE), Sjogren's syndrome, immune complex glomerulonephritis and other factors that affect C4 levels; and (5) subjects did not take drugs that affect uric acid levels before admission. A total of 169 hospitalized patients with NMOSD were selected. All patients met the international NMOSD diagnostic criteria in 2015.<sup>4</sup> As a retrospective study using anonymized data, this Ethics Committee of Zhengzhou University waived the need for informed consent. The study was reviewed and approved by the Ethics Committee of Zhengzhou University (ethics review number:2019-KY-018). We strictly abide by the "Declaration of Helsinki" and anonymized patient data.

### Patient Characteristics

The basic information of 169 patients was collected, including sex, age at first episode, symptoms onset to admission time, length of hospital stay, clinical manifestations, and treatment methods. The Expanded Disability Status Scale (EDSS) score was used to assess disease severity, which was evaluated by two neurologists. The patients were fasted for at least 12 hours after admission, and blood was drawn prior to treatment. All patients underwent 3.0 Tesla magnetic resonance imaging (MRI) examinations. The Neurology Laboratory of the First

Affiliated Hospital of Zhengzhou University used live cells transfected with AQP4 to detect the AQP4 antibody status in serum or cerebrospinal fluid samples. C4 levels were measured using a scattering turbidimetric method (reference value range: 0.14–0.44 g/L). Uric acid (UA) levels were measured through enzyme colorimetry (reference value range: 200–440  $\mu$ mol/L). According to the level of complement C4, patients were divided into a normal complement C4 group ( $\geq 0.14$  g/L) and a low complement C4 group ( $< 0.14$  g/L).

### Statistical Analysis

The SPSS Statistical Software (version 26.0, IBM Corp. Armonk: NY) was used for statistical analysis. Mean  $\pm$  standard deviation (SD) values were used to describe continuous variables conforming to the normal distribution, and the *t*-test was used for comparison between two groups. The median and interquartile range (IQR) were used to describe non-conformance normally distributed continuous variables, and the Mann–Whitney *U*-test was used to compare between two groups. Frequency and percentage were used to describe categorical variables, and the chi-squared test was used to compare categorical variables between two groups. Differences were considered statistically significant for values of  $p < 0.05$ .

## Results

### Basic Information and Clinical Features

A total of 169 AQP4 antibody positive subjects (49 men and 120 women) were included in this study. The male-to-female ratio was approximately 1:2, and the median age of the first-episode was 42 years. There were 54 patients in the low-complement C4 group, including 43 females (79.6%) and 11 males (20.4%), and 115 patients in the normal-complement C4 group, including 77 women (67%) and 38 men (33%). There was no significant difference in sex between the two groups ( $P > 0.05$ ). The median age of the low-complement C4 group was 43.5 years, and the median length of hospitalization was 18 days. The median age of the normal group was 41.5 years, and the median length of hospitalization was 19 days. There was no significant difference between the two ( $P > 0.05$ ). The median time from symptom onset to hospital admission was 12 days in both groups, and there was no statistically significant difference between the groups. Both the normal complement C4 group and the low complement C4 group showed symptoms of the five major clinical syndromes.

**Table I** Demographic Information and Clinical Characteristics of First-Episode NMOSD Patients in C4 Low-Level Group and Normal Group

Clinical Characteristics	C4 Normal Group	C4 Low-Level Group	P-value
Patients (n)	115	54	
Sex, n (%)			
Male	38(33)	11(20.4)	0.09
Female	77(67)	43(79.6)	
Age, years, median(IQR)	41.5(25–55)	43.5(28–51)	0.548
Length of hospital stay, days, median (IQR)	19(14–26)	18(12–27)	0.626
In the symptoms onset to admission time, days, median (IQR)	12(6–20)	12(7–24)	0.927
Clinical syndrome, n (%)			
Optic neuritis	32(27.8)	15(27.8)	0.995
Acute myelitis	83(72.2)	39(72.2)	0.995
Last area of medulla oblongata syndrome	11(9.6)	9(16.7)	0.183
Acute brain stem syndrome	19(16.5)	7(13)	0.55
Acute inter-brain syndrome	7(6.1)	2(3.7)	0.783
Brain syndrome	17(14.8)	11(20.4)	0.362

**Notes:** Statistical tests: Non-normally distributed continuous variables were presented as median (IQR = 25th–75th percentile), and categorical variables were described as percentages; The Mann–Whitney *U*-test was used for non-normally distributed measurement data, and the chi-square test was used for categorical variables.

**Abbreviations:** NMOSD, neuromyelitis optica spectrum disorder.

Acute myelitis was the most common condition. There was no statistically significant difference between the two groups in the five major clinical syndromes ( $P>0.05$ ) (Table 1).

## Cerebrospinal Fluid and Imaging Examinations

There was no significant difference between the two groups in cerebrospinal fluid (CSF) laboratory tests for white blood cell count, lymphocyte percentage, protein positive rate, or serum albumin ( $P>0.05$  for each measurement). However, serum immunoglobulin in the low complement C4 group was higher than that in the normal group (12.3 vs 10.5;  $P=0.029$ ). Based on anatomically informed subdivisions, we summarized the abnormal imaging findings of patients with optic neuromyelitis into five major parts: optic nerve, spinal cord, brainstem, diencephalon, and cerebrum. Twenty-nine (53.7%) patients in the low complement C4 group showed brainstem involvement, and 38 (33%) patients in the normal group showed brainstem involvement. A statistically significant difference was found between the number of cases involving the brainstem between the two groups (33% vs 53.7%;  $P=0.01$ ), though there was no statistically significant differences in the incidence of involvement for the remaining four anatomical areas ( $P>0.05$ ) (Table 2). The clinical manifestations of NMOSD were divided into last zone syndrome

and acute brainstem syndrome, and based on anatomical considerations, we collectively referred to last zone syndrome and acute brainstem syndrome as brainstem syndrome, which is convenient for statistical analyses. Of the 132 patients who did not show brainstem syndrome, 37 (28%) had brainstem abnormalities on imaging findings. Among the 37 patients with brainstem syndrome, 7 (6.9%) had negative brainstem imaging findings (Table 3).

## Disease Severity and Treatment Plan

There was no significant difference between the normal complement C4 group and the low complement C4 group in admission EDSS scores ( $P>0.05$ ), but the difference in the discharge EDSS scores was statistically significant (4 vs 4;  $P=0.019$ ). The median admission EDSS score was 5 for the normal complement C4 group and the low complement C4 group; the median of the discharged EDSS score was 4. During the acute phase of hospitalization, there was no statistically significant difference between the two groups in the use of one immunotherapy regimen alone or in combination with two or more immunotherapy regimens ( $P>0.05$ ) (Table 4).

## Clinicopathological Findings

Compared with the normal complement C4 group, routine blood values (white blood cell, red blood cell, haemoglobin, platelet, neutrophil, lymphocyte, monocyte count, neutrophil-

**Table 2** Results of Cerebrospinal Fluid and MRI Examinations in First-Episode NMOSD Patients in the Low-Level and Normal Groups of C4

Clinical Characteristics	C4 Normal Group	C4 Low-Level Group	P-value
Patients (n)	115	54	
CSF			
WBC, median (IQR), ( $10^6/L$ )	7(2–34)	4(2–26)	0.821
Lymphocyte, median (IQR), (%)	75.5(68–84)	76(70–81)	0.785
Protein-positive rates, n (%)	31(35.6)	16(39)	0.71
Immunoglobulin, median (IQR)			
CSF (mg/L)	40.3(23.4–66.0)	45.7(29.2–82.1)	0.091
Serum(g/L)	10.5(8.7–12.3)	12.3(9.5–17.1)	0.029*
Albumin, median (IQR)			
CSF (mg/L)	223.4(152.4–345.7)	247.8(137.3–400.3)	0.87
Serum(g/L)	41.5(39.3–44.7)	40.8(38.7–45.5)	0.561
MRI, n (%)			
Optic nerve	6(5.2)	3(5.6)	1
Spinal cord	92(80)	41(77.4)	0.695
Brain stem	38(33)	29(53.7)	0.01*
Diencephalon	5(4.3)	6(11.3)	0.173
Cerebrum	20(17.4)	15(27.8)	0.12

**Notes:** \* $P < 0.05$ ; Statistical tests: Non-normally distributed continuous variables were presented as median (IQR = 25th–75th percentile), and categorical variables were described as percentages; The Mann–Whitney *U*-test was used for non-normally distributed measurement data, and the chi-square test was used for categorical variables. **Abbreviations:** NMOSD, neuromyelitis optica spectrum disorder; CSF, cerebrospinal fluid; WBC, white blood cell; MRI, magnetic resonance imaging.

**Table 3** Brain Stem Syndrome and MRI Brain Stem Lesions

Brain Stem Lesions	Brain Stem Syndrome		Total
	Negative	Positive	
Negative	95	7	102
Positive	37	30	67
Total	132	37	169

**Abbreviation:** MRI, magnetic resonance imaging.

to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and lymphocyte-to-monocyte ratio) of the low complement C4 group were not statistically different ( $P > 0.05$ ), but the difference in eosinophils between the two groups was statistically significant (0.02 vs 0.07;  $P < 0.001$ ). The low complement C4 group showed a lower complement C3 level than the normal complement C4 group, and the difference between the two groups was statistically significant (0.87 vs 1.06;  $P < 0.001$ ). UA level in the low complement C4 group was lower than that in the normal group (179 vs 225;  $P = 0.001$ ) (Table 5).

## Discussion

NMOSD represents a group of inflammatory demyelinating diseases of the central system that is mainly mediated by humoral immunity, in which the complement also plays

**Table 4** Severity of Disease and Treatment Options in First-Episode NMOSD Patients in the Low-Level and Normal Groups of C4

Clinical Characteristics	C4 Normal Group	C4 Low-Level Group	P-value
Patients (n)	115	54	
EDSS, median (IQR)			
Initial	5(3–6)	5(4–7)	0.099
Discharge	4(2–5)	4(3–6)	0.019*
The acute treatment, n (%)			
One drug alone	97(84.3)	46(85.2)	0.888
Combination medication	18(15.7)	8(14.8)	

**Notes:** \* $P < 0.05$ ; Statistical tests: Non-normally distributed continuous variables were presented as median (IQR = 25th–75th percentile), and categorical variables were described as percentages; The Mann–Whitney *U*-test was used for non-normally distributed measurement data, and the chi-square test was used for categorical variables.

**Abbreviations:** NMOSD, neuromyelitis optica spectrum disorder; EDSS, Expanded Disability Status Scale.

a vital role.<sup>5–8</sup> Complement assays in clinical laboratories include the detection of C3 and C4 levels. We found that grouping by C3 levels, the main observation indicators between the groups were not statistically significant. In

**Table 5** Laboratory Test Results of First-Episode NMOSD Patients in C4 Low-Level Group and Normal Group

Clinical Characteristics	C4 Normal Group	C4 Low-Level Group	P-value
Patients (n)	115	54	
Blood routine			
WBC, median (IQR), ( $10^9/L$ )	6.7(5.2–9)	6.2(4.4–8.8)	0.143
RBC, $\bar{x} \pm s$ , ( $10^{12}/L$ )	4.3 $\pm$ 0.46	4.21 $\pm$ 0.65	0.298
Hb, $\bar{x} \pm s$ , (g/L)	127.17 $\pm$ 1.31	124.85 $\pm$ 1.95	0.323
PLT, median (IQR), ( $10^9/L$ )	225(183–274)	215(179–250)	0.201
Neutrophils, median (IQR), ( $10^9/L$ )	4.50(3.13–6.10)	4.01(2.93–5.82)	0.382
Lymphocyte, median (IQR), ( $10^9/L$ )	1.64(1.20–2.04)	1.26(1.05–2.02)	0.144
Monocytes, median (IQR), ( $10^9/L$ )	0.49(0.36–0.61)	0.44(0.29–0.60)	0.199
Eosinophils, median (IQR), ( $10^9/L$ )	0.07(0.03–0.14)	0.02(0.01–0.03)	<0.001*
NLR, median (IQR)	2.61(1.78–4.50)	2.92(1.66–4.69)	0.832
LMR, median (IQR)	3.80(2.40–5.08)	3.93(2.45–5.23)	0.891
NMR, median (IQR)	9.58(7.08–11.74)	8.52(6.67–16.65)	0.927
C3, median (IQR), (g/L)	1.06(0.94–1.20)	0.87(0.73–1.06)	<0.001*
Renal function			
Urea, median (IQR), (mmol/L)	4.50(3.58–5.75)	4.20(3.25–5.48)	0.505
Cr, median(IQR), ( $\mu$ mol/L)	53(46–61)	53(47–58)	0.854
Uric acid, median(IQR), ( $\mu$ mol/L)	225(177–287)	179(158–225)	0.001*

**Notes:** \* $P < 0.05$ ; Statistical tests: Continuous variables were presented as mean  $\pm$  SD or median (IQR = 25th–75th percentile; The t-test was used for normally distributed measurement data, and The Mann–Whitney U-test was used for non-normally distributed measurement data.

**Abbreviations:** NMOSD, neuromyelitis optica spectrum disorder; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; PLT, platelet; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte to monocyte ratio; NMR, neutrophil to monocyte ratio; Cr, Creatinine.

this study, we searched the literatures and found that the research related to C4 used the reference range of C4 level of the respective laboratory,<sup>10–12</sup> so we also used the reference range of the laboratory of our hospital to determine the grouping.

A total of 169 subjects were included in this study, and the male-to-female ratio was approximately 1:2, which was significantly higher than the results of a global NMOSD epidemiological survey.<sup>13</sup> Various studies have confirmed that the complement system is involved in autoimmune diseases, such as Sjogren's syndrome<sup>14</sup> and SLE.<sup>15</sup> Sjogren's syndrome and SLE are more common in female patients,<sup>16–18</sup> and NMOSD is often comorbid with the above-mentioned autoimmune diseases. The high male-to-female ratio in this study may be related to the elimination of patients with autoimmune diseases, such as Sjogren's syndrome and systemic lupus erythematosus. The median age of the patients included in this study was 42 years, which is consistent with the results of a global NMOSD epidemiological survey.<sup>13</sup> Of the 169 subjects, 122 (76.3%) had clinical manifestations of acute myelitis, indicating that the spinal cord was the most common site of involvement. However, there was no significant difference in

clinical manifestations between the two groups. It is speculated that complement abnormalities have no significant impact on clinical manifestations.

We summarized the abnormal imaging findings of NMOSD patients into five major regions: optic nerve, spinal cord, brain stem, diencephalon, and cerebrum, according to anatomical structure. By comparing the groups, we found that the difference between the two groups in the brainstem was statistically significant ( $P = 0.01$ ), suggesting that the brainstem is easily involved in patients with abnormal complement levels. We also compared the imaging findings with the clinical syndromes and found that approximately 28% of brainstem syndrome-negative patients showed brainstem lesions on imaging, and approximately 18.9% of brainstem syndrome-positive patients showed no signs of brainstem lesions. This indicated that, if conditions permit, it is necessary for clinicians to perform head MRI examinations, which may reveal more “invisible” lesions. However, the resolution limitations of MRI scanning may also lead to no remarkable observations. In such a case, the patient needs to be reviewed again, the medical history should be re-assessed, and evidence for brainstem syndrome must be investigated.



AQP-4 is highly expressed in the foot processes of astrocytes adjacent to the nerve vasculature and is particularly highly expressed in the brainstem, optic nerve, spinal cord, and periventricular regions.<sup>19</sup> The complement cascade can be activated through classical, alternative, or lectin pathways.<sup>20</sup> The AQP-4-IgG antibody binds to the antigen in the brainstem to form a large number of antigen-antibody complexes, and C1q recognizes the antibody-antigen complex to activate the classical pathway.<sup>20,21</sup> C1q cleaves C1r and activates the C1s protease to form the C1 complex (ie, C1qC1r2C1s2); C4 and C2 are then cleaved to form the classical pathway C3 convertase (C4bC2a), and the enzymatically active C4bC2a cleaves C3 to form two fragments of C3a and C3b, C3b combined with C4b2a to produce C4b2aC3b, and C5 convertase continues to activate downstream complement, finally completing the complement cascade reaction.<sup>20</sup> In this process, C4 is consumed; as such, we observed a decrease in serum complement C4 levels in clinical practice. However, some patients with NMOSD have normal complement C4 levels. By comparing the C3 levels of the two groups, it was found that low complement C4 was accompanied by low complement C3, and the C3 level of the normal complement C4 group was normal. As such, we speculate that not all patients with NMOSD have an activated complement system. Previous studies have shown that the brainstem is an important component of NMOSD, and a retrospective analysis showed that the incidence of brainstem lesions in NMOSD patients with serum AQP-4 antibody positivity was significantly higher than those with AQP-4 negativity, and that the recurrence rate was higher as well.<sup>22</sup> The brainstem maintains human breathing and heartbeat. The brainstem of low-complement C4 patients is more vulnerable than that of the normal complement group patients, indicating that these patients are at a high risk of respiratory and cardiac arrest, and that the condition is more dangerous. Clinicians should very carefully monitor these patients and identify signs of imminent danger over time.

We evaluated the EDSS scores of each patient on admission and discharge. The median values of the discharged EDSS scores of the two groups were the same, and the differences were statistically significant, suggesting that patients with low complement C4 had a poor prognosis. However, there was no significant difference in the treatment option. A total of 85.2% of patients with low complement C4 levels were treated with a single immunosuppressive method. The poor treatment effect of

the C4 group with low complement may be related to the single treatment regimen.

This study found that the eosinophil count in the low complement C4 group was significantly lower than that in the normal complement group. Previous studies have shown that C3a can indirectly stimulate neutrophils by activating eosinophils, while C5a is a chemotactic agent for both neutrophils and eosinophils.<sup>23</sup> After the classical complement activation pathway is activated, a large amount of C3a and C5a are produced at the lesion site, then eosinophils in the chemotactic serum cross the blood-brain barrier (BBB) and indirectly activate neutrophils.<sup>24</sup> After degranulation of granulocytes, the release of hydrolytic granzymes, bioactive lipids and superoxide anions may incur brain damage.<sup>24</sup> A study showed that the transgene expression of C3a in the central nervous system significantly exacerbated experimental autoimmune encephalomyelitis and caused inflammatory cell infiltration around blood vessels.<sup>25</sup> These results indicate that eosinophils play a key role in the pathogenesis of NMOSD.

UA, the end product of purine metabolism, is a natural water-soluble antioxidant that accounts for 60% of the free radical-scavenging activity in human blood, and it is a known scavenger of peroxynitrite (PN), also can be modified by drugs and diet.<sup>26–30</sup> Nitrogen oxide (NO) and its toxic metabolite PN are key mediators of nerve damage in Parkinson's disease.<sup>31</sup> PN is involved in the pathogenesis of central nervous system inflammatory diseases<sup>26</sup> and can cause DNA cleavage, lipid peroxidation, and oxidation and nitrication of amino acid residues and guanine. Hooper et al<sup>26</sup> proposed that UA may protect the permeability of the BBB by directly clearing PN. Another study showed that UA exerts its neuroprotective effect by eliminating the oxidative toxicity of PN and its downstream free radicals.<sup>32</sup> The plasma UA level is 10 times that of the CSF content and the two are positively correlated, indicating that UA is produced in the periphery and its penetration of the brain is restricted by the BBB. In other words, plasma UA and the integrity of the BBB jointly determine the CSF UA level.<sup>33</sup> Serum UA protects the integrity of the BBB, reduces its permeability, and can also reduce the infiltration of inflammatory cells, thereby reducing brain inflammation.<sup>34</sup> Previous studies have shown reduced serum UA levels in patients with NMOSD.<sup>35</sup> In this study, the blood UA level of the low complement C4 group was lower than that of the normal complement C4 group, indicating that the BBB damage and the infiltration of inflammatory cells

in patients with low complement levels were more serious.

With the in-depth exploration of the mechanism of NMOSD by researchers, people have reported novel markers for disease prediction, such as serum glial fibrillary acidic protein (sGFAP) and serum neurofilament light chain (sNfL). GFAP is mainly expressed by astrocytes and is an intermediate fibrous protein that forms the cytoskeleton of astrocytes.<sup>36</sup> NfL is a component of the neurofilament.<sup>37</sup> Nerve axon damage leads to the release of neurofilament, and then NfL can be detected in the cerebrospinal fluid and blood.<sup>38,39</sup> sGFAP levels and sNfL levels are closely related to EDSS score and age, and sGFAP levels are also closely related to the occurrence of recent relapse.<sup>40,41</sup> A multicenter, double-blind, randomized controlled trial showed that serum GFAP can be used as a biomarker of NMOSD activity, risk of disease, and treatment effect.<sup>41</sup>

Our study has certain limitations. First, this was a retrospective study, and therefore inherently biased. In addition, the number of cases included in the study was small. As such, multicenter, large-sample clinical studies are needed to further confirm this study's conclusions.

## Conclusion

In summary, AQP4 antibody-positive patients with low complement C4 levels have more severe damage to the blood-brain barrier, and changes in the disease easily involve the brainstem. Therefore, head MRI should be performed as frequently as is clinically possible. More multi-center large cohort studies are needed to further confirm.

## Disclosure

The authors report no conflicts of interest in this work.

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