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The clinical value of complement proteins in differentiating AQP4-IgG-positive from MOG-IgG-positive neuromyelitis optica spectrum disorders

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ABSTRACT

Background: Neuromyelitis optica spectrum disorder (NMOSD) refers to a range of autoimmune inflammatory demyelinating diseases affecting the optic nerves, spinal cord, and periependymal regions of the brain. Classical NMOSD is characterized by the presentation of autoantibodies against the water channel aquaporin-4 (AQP4). However, a subset of patients fulfilling the clinical criteria for NMOSD is negative for AQP4-IgG but positive for autoantibodies against myelin oligodendrocyte glycoprotein (MOG); these patients are associated with different clinical manifestations and pathogenesis.

Methods: Patients who received a first diagnosis of NMOSD were reviewed retrospectively between April 2015 and December 2018. Patients were classified according to the presence of AQP4-IgG and MOG-IgG in serum and/or cerebrospinal fluid. Clinical characteristics, magnetic resonance imaging findings, disease severity, and serum C3 and C4 levels at the first episode were compared between the groups.

Results: The NMOSD patients with AQP4-IgG and MOG-IgG demonstrated specific, differential clinical features. The AQP4-IgG group featured more women, the presentation of transverse myelitis attacks and simultaneous occurrence of optic neuritis and transverse myelitis were more common, and intrathecal synthesis was more evident. The MOG-IgG group featured younger patients, more acute disseminated encephalomyelitis (ADEM) or ADEM-like attacks, more frequent cerebrospinal fluid pleocytosis, and a better overall outcome. C3 levels were significantly lower in AQP4-IgG-positive patients and higher in MOG-IgG-positive patients relative to healthy controls. C4 levels were significantly lower in the AQP4-IgG-positive NMOSD group when compared to both MOG-IgG-positive patients and controls. C3 and C4 were then combined in a receiver operating characteristic model. The area under the curve of the model was calculated to differentiate the AQP4-IgG-positive group from the MOG-IgG-positive group was 0.787, which was considered moderately predictive.

Conclusion: The combination of C3 and C4 could assist in the differential diagnosis of AQP4-IgG-positive NMOSD from MOG-IgG-positive NMOSD.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) refers to a range of autoimmune inflammatory demyelinating diseases of the central nervous system, characterized by recurrent optic neuritis (ON) and transverse myelitis (TM) (Wingerchuk et al., 2015). The discovery of an NMO-specific antibody in 2004 (Lennon et al., 2004) allowed NMOSD patients to be distinguished from those with other demyelinating diseases, like multiple sclerosis (MS). The antibodies targeting aquaporin-4 (AQP4), which is present on the end-feet processes of astrocytes (Lennon et al., 2005), could cause astrocyte cytotoxicity, and consequently contribute to the disruption of the blood brain barrier, inflammatory responses within the central nervous system, and myelin breakdown (Papadopoulos and Verkman, 2012). There is substantial evidence that complement-mediated astrocyte damage drives the pathology underlying NMOSD; particularly in AQP4-IgG positive cases (Hakobyan et al., 2017), in which the NMO-induced loss of astrocytes is accompanied by the perivascular deposition of complement activation products (Lucchinetti et al., 2002; Roemer et al., 2007; Veszeli et al., 2014). However, a proportion of patients fulfilling the clinical criteria

Abbreviations: AQP4, aquaporin-4; ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; MOG, myelin oligodendrocyte glycoprotein; NMSOD, neuromyelitis optica spectrum disorder; ON, optic neuritis

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Table 1
Baseline characteristics of NMOSD patients and healthy controls.

	Healthy Control Male	Female	Total	AQP4-IgG-positive patients	MOG-IgG-positive patients	*P*-[a] value	*P*-[b] value	*P*-[c] value
Clinical characteristics								
Patients No.	22	0	51	67	27			
Female, n (%)	0	29	29 (56.9)	61 (91.4)	11 (40.7)	<0.001	0.059	0.155
Age, mean (SD)	51.6 (13.3)	42.7 (19.7)	46.5 (17.8)	42.8 (14.7)	31.8 (13.7)	0.022	<0.001	0.001
Onset attack, *n* (%)								
ON	NA	NA	NA	13 (19.4)	7 (25.9)			0.490
TM	NA	NA	NA	27 (40.3)	5 (18.5)			0.044
ADEM or ADEM-like (including brainstem attacks)	NA	NA	NA	12 (17.9)	15 (55.6)			0.000
Simultaneous ON and TM	NA	NA	NA	15 (22.4)	0 (0)			0.007
Clinical status								
pre-treatment EDSS, median (IQR)	NA	NA	NA	5.5 (4.5–7)	4 (3.25–4.75)			0.000
post-treatment EDSS, median (IQR)	NA	NA	NA	4.5 (3.5–6)	3 (2–3.75)			0.001
Laboratory data								
AQP4-IgG titer, median (IQR)	0	0	0	100 (32–320)	0			
MOG-IgG titer, median (IQR)	0	0	0	0	10 (10–21)			
C3 (g/L)	0.87 (0.15)	0.86 (0.17)	0.86 (0.16)	0.79 (0.18)	0.98 (0.28)	0.016	0.006	<0.001
C4 (g/L)	0.21 (0.06)	0.20 (0.06)	0.21 (0.06)	0.18 (0.06)	0.21 (0.07)	0.005	0.868	0.040
CSF findings, n (%)								
CSF cell (>10/μL)	0(0) (*n* = 21)	0(0) (*n* = 27)	0(0) (*n* = 48)	15(27.8) (*n* = 54)	11(44.0) (*n* = 25)	0.003	<0.001	0.009
CSF protein (>0.6 g/L)	3(14.3) (*n* = 21)	5(18.5) (*n* = 27)	8(16.7) (*n* = 48)	9(16.7) (*n* = 54)	4(16.0) (*n* = 25)	1.000	0.943	0.942
CSF oligoclonal bands	0(0) (*n* = 14)	0(0) (*n* = 21)	0(0) (*n* = 35)	0(0) (*n* = 47)	0(0) (*n* = 21)	1.000	1.000	1.000
CSF IgG index >0.7	0(0) (*n* = 12)	1(8.3) (*n* = 12)	1(4.2) (*n* = 24)	17(40.5) (*n* = 42)	3(15.0) (*n* = 20)	0.001	0.223	0.046

Data are shown as mean (SD), median (IQR) for continuous variables, and as percentages for categorical variables.
ON, optic neuritis; TM, transverse myelitis; ADEM, acute disseminated encephalomyelitis; EDSS, Expanded Disability Status Scale; AQP4-IgG, seropositive for IgG against aquaporin-4; MOG-IgG, seropositive for IgG against myelin oligodendrocyte glycoprotein; CSF, cerebrospinal fluid; NA, not applicable.
[a] AQP4-IgG-positive patients with NMOSD versus healthy controls.
[b] MOG-IgG-positive patients with NMOSD versus healthy controls.
[c] AQP4-IgG-positive patients with NMOSD versus MOG-IgG-positive patients with NMOSD.

for NMOSD are AQP4-IgG negative (Hakobyan et al., 2017; Jarius and Wildemann, 2010). Some of these AQP4-seronegative patients have been shown to exhibit autoantibodies against myelin oligodendrocyte glycoprotein (MOG) and are associated with pathological evidence of demyelination without astrocyte loss (Spadaro et al., 2015), suggesting a different underlying pathogenesis. The clinical significance of complement activation in MOG-IgG-positive NMOSD is yet to be elucidated. A retrospective study found definite differences in complement function between AQP4-IgG-positive NMOSD patients and healthy controls, even during remission (Veszeli et al., 2014). Another study demonstrated that peripheral complement activation, evinced by altered plasma markers, is markedly increased in AQP4-IgG positive NMOSD, enabling its differentiation from MS (Hakobyan et al., 2017). We sought to evaluate the clinical value of complement proteins in AQP4-IgG-positive or MOG-IgG-positive NMOSD patients with an independent cohort.

2. Materials and methods

2.1. Subjects

Medical registries of Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology were reviewed retrospectively between April 2015 and December 2018. Data from seropositive NMOSD patients (with AQP4-IgG or MOG-IgG), diagnosed based on 2015 criteria for NMOSD (Wingerchuk et al., 2015) were analyzed. Patients who measured C3/C4 during their first attack of NMOSD before therapeutic intervention were enrolled. This study was approved by the Institutional Review Board at Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology. Written informed consents were obtained from all patients or their authorizer.

2.2. AQP4-IgG, MOG-IgG, C3 and C4

AQP4-IgG and MOG-IgG were detected with a cell-based assay (Lennon et al., 2004). Serum C3 and C4 levels were measured during their first attacks and diagnostic procedures of NMOSD. The average (± SD) period of time between onset of attack and measurement of C3/C4 is 12.5 ± 9.3 days for AQP4-IgG positive patients, and 13.2 ± 9.5 days for MOG-IgG positive patients.

2.3. Studied variables

Patients were classified according to the presence of AQP4-IgG and MOG-IgG in the serum and/or cerebrospinal fluid (CSF). Clinical characteristics, MRI findings, and serum levels of C3 and C4 at the first attack were compared between the groups. Clinical statuses before and after treatment were examined with the Expanded Disability Status Scale (EDSS) score.

2.4. Statistical analysis

Different groups were compared using the Mann-Whitney U test or two-way ANOVA with Dunnett's post-hoc test. Data were compared between different groups using the log-rank test. Variables with two-tailed *p*-values of <0.05 were considered significant. All statistical analyses were performed using SPSS software (version 21; SPSS Inc., Chicago, IL).

3. Results

During the study period, 139 patients were diagnosed with AQP4-IgG-positive NMOSD, and 58 patients were diagnosed with MOG-IgG-positive NMOSD for the first time. Of these, 67 (48.2%) AQP4-IgG-positive and 27 (46.5%) MOG-IgG-positive NMOSD patients who underwent complement protein (C3 and C4) tests before clinical

intervention were enrolled. Healthy individuals ($n = 51$) presenting for a health screen served as controls (Table 1).

The median age at onset was 48.2 years (SD, 14.7) in AQP4-IgG-positive patients and 31.8 years (SD, 13.7) in MOG-IgG-positive patients. The median AQP4-IgG titer was 1:100 (IQR, 1:32–1:320) and the median MOG-IgG titer was 1:10 (IQR, 1:10–1:21). For the 67 AQP4-IgG positive patients, the following were recorded during the onset attack in the registry: 13 ON, 27 TM, 12 acute disseminated encephalomyelitis (ADEM) or ADEM-like attacks (including brainstem attacks), and 15 simultaneous TM and ON. For the 27 MOG-IgG positive patients, the following were recorded during the onset attack in the registry: 7 ON, 5 TM, 15 ADEM or ADEM-like, and no simultaneous TM and ON at onset. The AQP4-IgG-positive group was more likely to experience TM or both TM and ON, and the MOG-IgG-positive group suffered more from ADEM or ADEM-like attacks. Clinical status (including pre- and post-treatment EDSS) showed the severity and disability at the first attack was less severe, and the prognosis after treatment better for MOG-IgG-positive patients than for AQP4-IgG-positive patients. The AQP4-IgG positive group tended to have fewer cells in the CSF and more intrathecal synthesis of IgG than the MOG-IgG positive group (Table 1).

Differences in the levels of the complement proteins C3 and C4 among AQP4-IgG-positive patients, MOG-IgG-positive patients, and healthy controls showed a clear trend. Compared with healthy controls, C3 levels were significantly decreased in AQP4-IgG-positive patients but greatly increased in MOG-IgG-positive patients. C4 levels were significantly lower in the AQP4-IgG-positive NMOSD group than both the MOG-IgG-positive NMOSD and control groups (Table 1, Fig. 1). Statistical analysis demonstrated that each of the two complement analytes measured significantly distinguished AQP4-IgG-positive NMOSD patients from their MOG-IgG-positive counterparts. C3 and C4 were then combined in a receiver operating characteristic model. The AUC of the model used to differentiate the AQP4-IgG-positive group from the MOG-IgG-positive group combining C3 and C4 was 0.787, which was considered moderately predictive (Fig. 1).

4. Discussion

In agreement with previous studies (Hoftberger et al., 2015; Kitley et al., 2014; Sato et al., 2014), our study found that NMOSD patients who were positive for either AQP4-IgG and MOG-IgG with characterized by specific clinical features: The proportion of women was higher among patients with AQP4-IgG (91.4%) than those with MOG-IgG (40.7%). Patients in the MOG-IgG group were younger age (31.8 years) than those in the AQP4-IgG group (42.8 years). TM attacks and the simultaneous occurrence of ON and TM were more common among AQP4-IgG patients, and more ADEM or ADEM-like attacks (including brainstem attacks) were observed in MOG-IgG patients at onset. CSF pleocytosis was more frequent in MOG-IgG-positive patients (44%) than in AQP4-IgG patients (27.8%). Less evidence of intrathecal synthesis of IgG, as assessed by the IgG index, was found in MOG-IgG patients, and patients with MOG-IgG were shown to have a better overall outcome as measured by the EDSS score. However, the degree of improvement after the first attack was not significantly different between the two groups.

Multiple studies examining the roles of complement proteins in the pathology of NMOSD have indicated that complement activation drives the pathology of classical AQP4-IgG-positive NMOSD; this finding enables the reliable diagnosis of NMOSD (Veszeli et al., 2014) and its differentiation from MS (Hakobyan et al., 2017). However, the difference between NMOSD patients positive for AQP4-IgG or MOG-IgG has received relatively scant attention in the literature. In our cohort, comparing AQP4-IgG-positive patients, MOG-IgG-positive patients, and healthy controls showed that C3 levels were significantly lower in the AQP4-IgG group and much higher in MOG-IgG group than in the control group, and that C4 levels were significantly lower in the AQP4-IgG group than in the MOG-IgG and control groups. The results of this study thus support the diagnostic value of C3 and C4 levels in differentiating AQP4-IgG-positive from MOG-IgG positive patients.

Prevailing hypotheses posit that anti-AQP4 antibodies induce astrocyte cytotoxicity and, consequently, the demyelination characteristic of NMOSD (Veszeli et al., 2014). The pathogenic effects of AQP4-IgG binding to astrocytes are primarily thought to activate the complement system and cause the deposition of the membrane-attack complex rather than the direct disruption of AQP4 function (Papadopoulos and Verkman, 2012; Pilch et al., 2017). The major part of complement activation ends with C3 deposition and the subsequent generation of soluble complement fragments, which can act as potent inflammatory mediators (Pilch et al., 2017). The inflammatory response recruits granulocytes, causes astrocytic and oligodendrocytic death that further results in demyelination, axonal degeneration, and finally neuronal death (Papadopoulos et al., 2014). While the mechanisms underpinning these changes remains unclear, it likely involves increased consumption of complements; hence, we observed decreased levels of serum C3 and C4 in AQP4-IgG-positive NMOSD patients relative to both controls and MOG-IgG-positive NMOSD patients.

On the other hand, the C3 levels of MOG-IgG-positive NMOSD patients increased significantly relative to those of controls, while differences in the levels of C4 between the two groups were nonsignificant. Moreover, the significant difference in C3 and C4 levels between AQP4-IgG-positive and MOG-IgG-positive NMOSD patients suggests differential complement participation. While the pathological hallmark of AQP4-IgG-positive NMOSD is astrocytic damage with secondary oligodendrocyte loss and demyelination (Dos Passos et al., 2018), no evidence of astrocytopathy has been reported in cases of MOG-IgG-induced demyelination.

In MOG-IgG NMSOD cases, lesions have been described as clearly demyelinating with the relative preservation of axons and astrocytes, the marked infiltration of macrophages and lymphocytes, and the depositions of IgG and complement proteins (Dos Passos et al., 2018; Spadaro et al., 2015). The majority of anti-MOG antibodies identified have been of the IgG1 isotype, which is able to initiate both

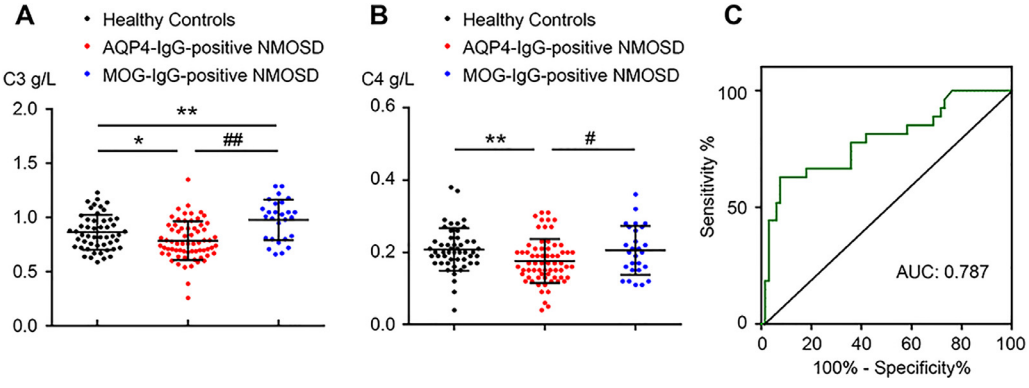

Fig. 1. Serum levels of C3 and C4 differentiate MOG-IgG positive and AQP4-IgG positive NMOSD patients.
(A–B) Serum levels of C3 and C4 in MOG-IgG-positive NMOSD patients, AQP4-IgG-positive NMOSD patients, and healthy controls. $^{*}P < 0.05$, $^{**}P < 0.01$ versus healthy controls, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ versus AQP4-IgG positive NMOSD. **(C)** C3 and C4 levels combined in a receiver operating characteristic model with an area under the curve value of 0.787.

complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity in an Fc-dependent manner (Peschl et al., 2017; Ramanathan et al., 2016). To summarize previous findings, MOG associated pathology is mediated by lymphocytes and complement-fixing antibodies. The precise functions of the complement system in MOG-IgG positive patients and how it differs from its role in AQP4-IgG-positive patients remain to be elucidated.

The present study was subject to several limitations. The small sample size and the retrospective nature of the study indicate that biases are inevitable. Moreover, all patients were ethnically Chinese; our results may not apply to other populations. While complement analytes have been tested in a number of studies and proven to be highly predictive of NMOSD (Hakobyan et al., 2017; Veszeli et al., 2014), but none has yet allowed for the differentiation of patients with AQP4-IgG from those with MOG-IgG. Our findings suggest that complement activation occurs in both groups but in a significantly different manner. Further research on the pathophysiology of the complement system in MOG-IgG-mediated demyelination is needed to elucidate details concerning complement proteins and the activation products in MOG-IgG NMOSD and thereby better differentiate the condition from classical NMOSD patients. Moreover, C3 or C4 consumption in NMOSD might be related to the length of extent of a lesion. Whether the difference in clinical presentations between the two groups results in the difference of complement consumption needs further investigation. The development of effective treatments for MOG-IgG-positive patients and its assessment in clinical trials are also warranted.

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Conflict of interest

The authors have declared that no competing interest exists.

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