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Different Complement Activation Patterns Following C5 Cleavage in MOGAD and AQP4-IgG+NMOSD

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Abstract

Objectives

In myelin oligodendrocyte glycoprotein IgG–associated disease (MOGAD) and aquaporin-4 IgG+ neuromyelitis optica spectrum disorder (AQP4+NMOSD), the autoantibodies are mainly composed of IgG1, and complement-dependent cytotoxicity is a primary pathomechanism in AQP4+NMOSD. We aimed to evaluate the CSF complement activation in MOGAD.

Methods

CSF-C3a, CSF-C4a, CSF-C5a, and CSF-C5b-9 levels during the acute phase before treatment in patients with MOGAD (n = 12), AQP4+NMOSD (n = 11), multiple sclerosis (MS) (n = 5), and noninflammatory neurologic disease (n = 2) were measured.

Results

CSF-C3a and CSF-C5a levels were significantly higher in MOGAD (mean ± SD, 5,629 ± 1,079 pg/mL and 2,930 ± 435.8 pg/mL) and AQP4+NMOSD (6,017 ± 3,937 pg/mL and 2,544 ± 1,231 pg/mL) than in MS (1,507 ± 1,286 pg/mL and 193.8 ± 0.53 pg/mL). CSF-C3a, CSF-C4a, and CSF-C5a did not differ between MOGAD and AQP4+NMOSD while CSF-C5b-9 (membrane attack complex, MAC) levels were significantly lower in MOGAD (17.4 ± 27.9 ng/mL) than in AQP4+NMOSD (62.5 ± 45.1 ng/mL, $p = 0.0019$). Patients with MOGAD with severer attacks (Expanded Disability Status Scale [EDSS] ≥ 3.5) had higher C5b-9 levels (34.0 ± 38.4 ng/m) than those with milder attacks (EDSS ≤3.0, 0.9 ± 0.7 ng/mL, $p = 0.044$).

Discussion

The complement pathway is activated in both MOGAD and AQP4+NMOSD, but MAC formation is lower in MOGAD, particularly in those with mild attacks, than in AQP4+-NMOSD. These findings may have pathogenetic and therapeutic implications in MOGAD.

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Introduction

Myelin oligodendrocyte glycoprotein IgG–associated disease (MOGAD) and aquaporin-4 IgG-positive neuromyelitis optica spectrum disorder (AQP4+NMOSD) are inflammatory diseases of the CNS. In these diseases, Th17-related cytokines/chemokines are remarkably upregulated in acute exacerbations[1] and clinical phenotypes such as optic neuritis (ON) or longitudinally extensive myelitis may occur. Both MOG-IgG and AQP4-IgG are mainly composed

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of IgG1,[2] which can efficiently activate complements. Complement-dependent cytotoxicity (CDC) is a key pathomechanism in AQP4+NMOSD,[3] and anti-complement C5 monoclonals are highly effective in preventing relapse of AQP4+NMOSD. However, the pathogenetic role of complement activation in MOGAD remains unclear.

This study aimed to investigate complement activation in the CSF of patients with MOGAD relative to AQP4+NMOSD.[4]

Methods

CSF samples were collected from adults with MOGAD, AQP4+NMOSD, multiple sclerosis (MS), and noninflammatory neurologic disease (NIND) between 2018 and 2023. All samples from patients with MOGAD, AQP4+NMOSD, and MS were obtained before acute-phase treatments. Their clinical and laboratory data were also collected.

CSF samples were stored at −80°C until use. C3a, C4a, and C5a were measured using a bead-based assay (Human Anaphylatoxin Kit, BD, San Jose, CA) and C5b-9 by an ELISA (Human C5b-9 ELISA Set, BD, San Jose, CA) according to the manufacturers' protocol. MOG-IgG and AQP4-IgG were measured with in-house cell-based assays as previously reported.[5]

All parameters were compared among MOGAD, AQP4+-NMOSD, MS, and NIND groups using the Kruskal-Wallis test. Statistical analyses were performed using PRISM 8.0 (GraphPad Software, Boston, MA). Data are available to qualified researchers based on reasonable request.

Ethics approval was granted by the Ethics Committee of Tohoku University Graduate School of Medicine, Sendai, Japan (#2022-1-1103). All the patients gave informed consent for their participation.

Results

Clinical Profiles of the Patients

In total, 30 patients with MOGAD (n = 12), AQP4-IgG+NMOSD (n = 11), MS (n = 5), or NIND (n = 2) were studied (Table 1). The mean age was significantly lower in the MOGAD group (median 32 years; range, 17–68 years) than in the AQP4+NMOSD group (59, 34–76 years) (p = 0.010). Approximately two-thirds of patients with MOGAD and AQP4+NMOSD were female. The most frequent clinical phenotype in patients with MOGAD (33.3%) and AQP4+-NMOSD (63.6%) was myelitis. Among patients with MOGAD, AQP4+NMOSD, and MS, there were no significant differences in the percentage of the first attack at sample collection, interval from onset to sample collection, and Expanded Disability Status Scale (EDSS) scores at the acute phase and last follow-up. 3 patients with MOGAD had CSF-restricted MOG-IgG. All patients met respective diagnostic criteria.[6,7]

CSF Complement Levels

CSF-C3a, CSF-C4a, CSF-C5a, and CSF-C5b-9 levels are shown in Figure 1, A–D and the Table 1. C3a and C5a were significantly higher in MOGAD and AQP4+NMOSD than in MS, and C5a was significantly higher in MOGAD than in NIND. There were no differences in C3a, C4a, and C5a between MOGAD and AQP4+NMOSD. However, C5b-9 (membrane attack complex, MAC) was significantly lower in MOGAD than in AQP4+NMOSD (p = 0.002).

Terminal Complement Pathway Activation Patterns Differ Between MOGAD and AQP4+NMOSD

C5 is cleaved into C5a and C5b, which is followed by C5b-9 assembly. Therefore, we calculated the C5b-9/C5a ratios to assess terminal complement pathway activation after C5 cleavage. The CSF-C5b-9/C5a was significantly lower in MOGAD (mean ± SD, 17.4 ± 27.9) than in AQP4+NMOSD (62.5 ± 45.1, p = 0.0019) (Figure 1E).

Patients with higher EDSS scores (EDSS during attacks ≥3.5) had significantly higher CSF-C5b-9 than those with low EDSS scores (EDSS≤ 3.0) (p = 0.030) (Figure 1F). Furthermore, patients with high EDSS scores at the last follow-up (≥3.5, n = 3) tended to have higher CSF-C5b-9 (34.0 ± 38.4 ng/mL) than those with low EDSS scores (≤3.0, n = 8, 0.90 ± 0.72 ng/mL, p = 0.064).

There was no significant difference among data related to clinical phenotypes and MOG-IgG status in sera and CSF (Figure 2 and eTable 1). C5b-9 values were not different in relation to MOG-IgG status in sera and CSF. However, especially for clinical phenotypes, in both myelitis and others, the mean C5b-9 values tended to be lower in MOGAD than in AQP4+NMOSD.

Discussion

We demonstrated that CSF-C3a and CSF-C5a levels during the acute phase in MOGAD were comparable with those in AQP4+NMOSD and higher than those in MS and NIND. We previously reported CSF complement activation in AQP4+-NMOSD compared with NIND.[4] Anaphylatoxin effects of C3a and C5a may contribute to CSF pleocytosis in MOGAD and AQP4+NMOSD and be part of MOGAD pathology even if downstream MAC formation is not present in all patients. Meanwhile, CSF-C5b-9 levels, indicative of MAC formation, were significantly lower in MOGAD than those in AQP4+NMOSD.

It was reported that increased levels of proteins indicative of systemic classical and alternative complement activation in the plasma of adult and pediatric patients with MOGAD (n = 71) compared with relapsing MS, AQP4+NMOSD, and healthy controls.[8] More recently, Cho et al. reported complement activation in sera of MOGAD,[9] but C5b-9 was not elevated

Table 1 Clinical, Laboratory Profiles and Complement Levels of Patients With MOGAD, AQP4-IgG+NMOSD, MS, and NIND

	MOGAD (n = 12)	AQP4-IgG+NMOSD (n = 11)	MS (n = 5)	NIND (n = 2)
Clinical, laboratory profiles				
Median age at sampling (years old)	32	59	32	42.5
Female sex (%)	66.6	63.6	100	100
Clinical phenotype	Myelitis (n = 4)	Myelitis (n = 7)	Relapsing-remitting (n = 5)	Idiopathic NPH (n = 1)
	ADEM (n = 3)	Optic neuritis (n = 2)		Psychogenic functional neurologic disorder (n = 1)
	Encephalitis (n = 3)	Area postrema syndrome (n = 1)		
	Optic neuritis (n = 2)	Diencephalic syndrome (n = 1)		
First attack (%)	66.7	54.5	N/A	N/A
Interval from onset to sampling (d)	17.5	12	22	N/A
EDSS at sampling	3.5 (1–7.5)	3 (2–7.5)	2 (1–5.5)	N/A
CSF cell count (/mm^3)	6.5 (0–256)	10 (0–93)	1 (1–4)	0
CSF protein (mg/dL)	38.5 (19–123)	32 (19–210)	28 (20–41)	27 (26–28)
IgG index	0.54 (0.45–2.06)	0.57 (0.43–0.84)	0.71 (0.52–1.99)	N/A
OCB positivity (%)	33.3	27.2	100	N/A
Complement levels				
C3a (pg/mL)	5,624 ± 1,079	6,017 ± 3,937	1,507 ± 1,286	1947 ± 2,620
C4a (pg/mL)	115.2 ± 190.2	74.86 ± 144.8	1.756 ± 3.927	15.77 ± 22.31
C5a (pg/mL)	2,930 ± 435.8	2,544 ± 1,231	193.8 ± 0.53	777.5 ± 880.8
C5b-9 (ng/mL)	17.42 ± 27.92	62.48 ± 45.11	22.35 ± 4.239	22.46 ± 0.444

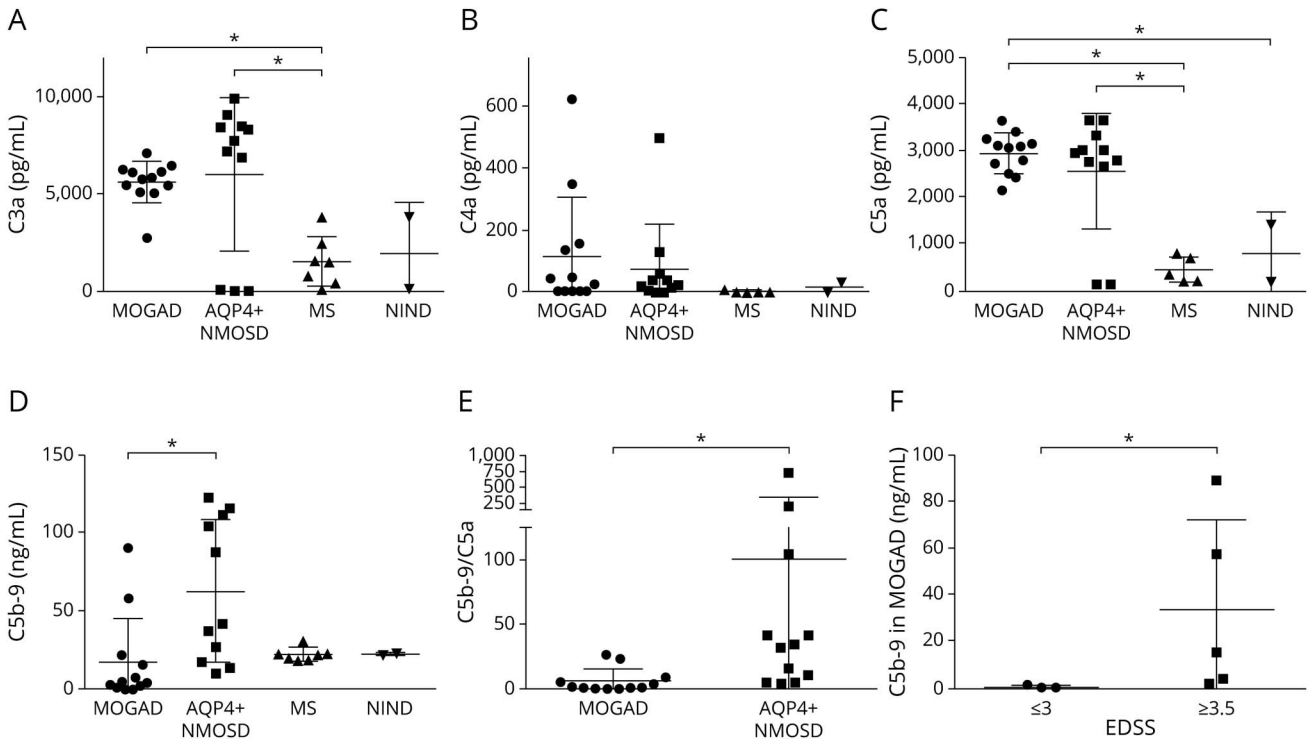
Abbreviations: ADEM = acute disseminated encephalomyelitis, AQP4-IgG+NMOSD = aquaporin 4-IgG-positive neuromyelitis optica spectrum disorder, EDSS = Expanded Disability Status Scale, MOGAD = myelin oligodendrocyte glycoprotein IgG–associated disease, MS = multiple sclerosis, NIND = noninflammatory neurologic disease, NPH = normal pressure hydrocephalus, OCB = oligoclonal IgG band.
Values are presented as mean ± SD.

compared with AQP4+NMOSD, which is similar to our result. Nevertheless, the studies analyzed only blood samples, which may not necessarily reflect complement activation in the CNS.

In vitro studies performed by Yandamuri et al. and Kohyama et al. demonstrated that MOG-IgG can induce CDC in MOG-transfected cells, depending on the amount of complement proteins or MOG-IgG titer.[10,11] Furthermore, Macrini et al.[12] reported that MOG-IgG requires bivalent binding to MOG monomers and C1q, an initiator of the classical complement pathway, poorly binds to MOG-IgG-MOG complexes, suggesting that CDC may not be a major pathomechanism in MOGAD. Lerch et al. showed that MOG-IgG can induce CDC in MOG-transfected HEK293A cells; however, CDC and MAC formation levels were significantly lower than those induced in AQP4-transfected HEK293A cells by AQP4-IgG.[13] In line herewith, our histopathologic study in MOGAD and AQP4+NMOSD clearly demonstrated that C9neo was deposited at substantially lower levels in acute MOGAD lesions than in AQP4-NMOSD.[14] By contrast, Höftberger et al. reported that activated complement deposition in lesions was more or less observed in all cases with MOGAD.[15] The reason is unclear, but difference in detection methods and patient backgrounds might have contributed.

An interesting but perplexing finding in our study was that CSF-C5b-9 levels were significantly lower in MOGAD than those in AQP4+NMOSD, although the complement cascade leading to C5 in CSF was equally activated in MOGAD and AQP4+-NMOSD. CD59 is the only complement-regulatory protein on the surface of human cells that inhibits MAC formation.[16] In the CNS, CD59 is abundantly expressed on the outer layer of myelin, whereas it is weakly expressed on astrocyte foot process.[17,18] Considering that MOG is mainly expressed on the outer layer of myelin and AQP4 is richly expressed on astrocyte foot processes, CD59 on myelin might inhibit MAC formation more efficiently in MOGAD than in AQP4+NMOSD. However, myelin vs astrocyte may not per se explain the significantly lower CSF-C5b-9 levels in MOGAD than in AQP4-NMOSD as

Figure 1 CSF Complement Components in MOGAD, AQP4+NMOSD, MS, and NIND



(A–E) Concentrations of activated complement components (C3a, C4a, C5a, C5b-9) and C5b-9/C5a in the CSF of patients with MOGAD, AQP4+NMOSD, MS, and NIND and (F) comparison of CSF-C5b-9 levels between patients with MOGAD with EDSS scores ≦3 and those with scores ≧3.5. AQP4+NMOSD = aquaporin-4 IgG+ neuromyelitis optica spectrum disorder, MOGAD = myelin oligodendrocyte glycoprotein IgG–associated disease, MS = multiple sclerosis, NIND = noninflammatory neurologic disease. $*p < 0.05$. Horizontal lines indicate mean values, and error bars indicate SD.

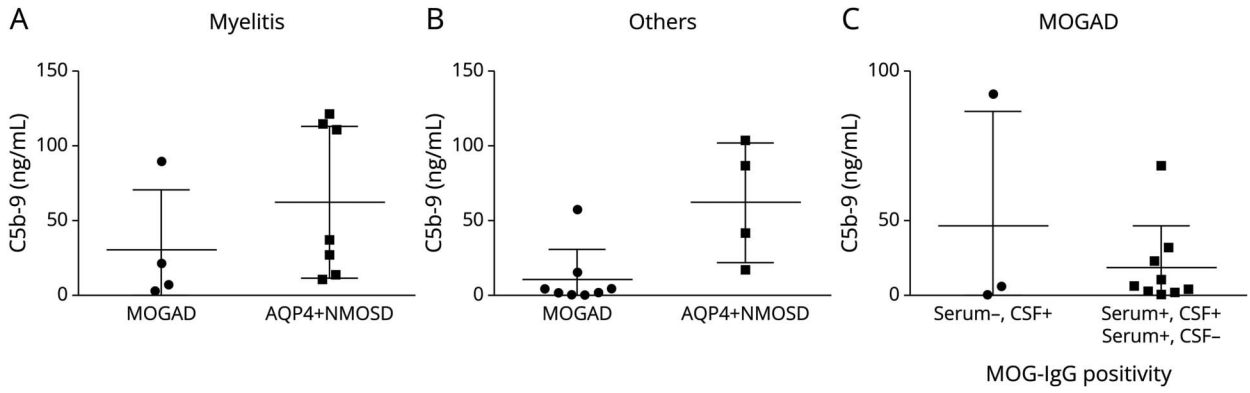
observed in our study because, in the study by Lerch et al., both CDC and MAC were induced in HEK293A cells by MOG-IgG and AQP4-IgG,[10] suggesting that other factors are involved in the distinct MAC formations in the 2 diseases.

From a therapeutic viewpoint, our results suggest that currently available anti-C5 monoclonal antibodies may not be as effective in MOGAD as in AQP4+NMOSD, although it might be beneficial for patients with severe attacks and high CSF-C5b-9 values.

The main limitations of this study were small sample size, especially ON, the lack of comparison with remission phase, and the insufficient involvement of pediatric cases. Larger scale clinical studies to address these issues are needed.

In summary, the complement pathway is activated in both MOGAD and AQP4+NMOSD, but MAC formation seems to be lower in MOGAD, particularly in cases with mild attacks, than in AQP4+NMOSD. Our findings may have pathogenetic and therapeutic implications in MOGAD.

Figure 2 CSF-C5b-9 Levels in Relation to Clinical Phenotypes and MOG-IgG Status



AQP4+NMOSD = aquaporin-4 IgG+ neuromyelitis optica spectrum disorder, MOGAD = myelin oligodendrocyte glycoprotein IgG–associated disease.

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Disclosure

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Continued

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