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Brief Report

Clinical Significance of Myelin Oligodendrocyte Glycoprotein Autoantibodies in Patients with Typical MS Lesions on MRI

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Abstract

Background: Myelin-oligodendrocyte-glycoprotein (MOG)-IgG-positivity in patients with typical MS lesions on MRI may lead to diagnostic/therapeutic uncertainty.

Objective and Methods: We reviewed reports of cases with MS phenotype on MRI and MOG-IgG-positivity published in Pubmed between 01/2012–06/2021.

Results: Sixteen patients were included (median age [range], 37,5 [25–66] years; 60% female). Three patients initially tested negative for MOG-IgG. Disease course was: relapsing-remitting, 10; or progressive, 6. Intrathecal IgG-synthesis was common (79%). Low and high-efficacy MS-targeted agents prevented relapses in 30% and 100%, respectively. None of the patients showed resolution of MRI T2-lesions over time.

Conclusions: MOG-IgG-positivity is unlikely to alter the expected treatment response and outcomes in patients with otherwise typical MS phenotype on MRI.

Keywords: MOG-IgG, MOGAD, MS, NMOSD, false positive

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Introduction

Myelin oligodendrocyte glycoprotein-IgG-associated disorder (MOGAD) is a recently defined demyelinating disease of the CNS, distinct from MS and aquaporin-4-IgG-positive neuromyelitis optica spectrum disorder (AQP4-IgG-NMOSD).[1–3] Serum positivity for MOG-IgG by cell-based assays confirms the diagnosis in patients with compatible clinical-MRI phenotypes, including acute/subacute attacks of optic neuritis (generally recurrent or bilateral), myelitis (commonly accompanied by a longitudinally-extensive T2-hyperintensity on MRI), and/or brain inflammation (typically accompanied by large MRI lesions or cortical involvement with encephalitis).[2] However, MOG-IgG positivity may occasionally occur in patients with typical MS lesions on MRI.[4] Although MOG-IgG is assumed to be a false positive result in such patients, some have suggested they might represent atypical manifestations of MOGAD. In this systematic review, we studied the clinical characteristics, treatment response, and outcomes in patients with typical MS lesions on MRI and MOG-IgG positivity.

Methods

A search of the English literature was conducted in PubMed by two neurology residents (P.Z.; V.F.) from January 01, 2012 (year of the earliest MOGAD descriptions)[3] through June 30, 2021, using the terms "MOG", "MOGAD" or "myelin oligodendrocyte glycoprotein". A total of 3031 articles underwent screening for eligibility. Inclusion criteria were: 1) presence of typical MS lesions on the brain MRI images provided in the included studies, confirmed by two neurologists (E.S., A.S.L.);[5] 2) MOG-IgG positivity assessed by a cell-based assay (fixed or live); and 3) sufficient clinical details. Patients with longitudinally extensive T2-lesions on

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spinal cord MRI were excluded.[6] Clinical and laboratory characteristics were abstracted.

Results

Sixteen patients were included (Table 1) from nine articles (Supplementary Table). The median age was 37,5 years (range, 25–66); 9/15 (60%) were female (gender not available for one case).

Clinical-MRI characteristics

All cases fulfilled the 2017 McDonald's MS diagnostic criteria,[7] except for MOG-IgG positivity; none met international recommendations for MOG-IgG testing due to the presence of typical MS abnormalities on brain MRI.[2] The clinical course was: relapsing-remitting, 10 (63%), primary progressive, 5 (31%) or secondary progressive, 1 (6%). Clinical attacks were not preceded by infections/vaccinations.

MRI T2-abnormalities affecting both brain and spinal cord were reported in 15/16 (94%), while 1 patient had lesions exclusively in the brain. Serial MRIs, available in 10/16 (63%), showed stable T2-lesion load in 6/10 (60%) and new asymptomatic T2-lesions in 4/10 (40%).

CSF

Among those with available CSF findings, >2 CSF-restricted oligoclonal bands and/or elevated IgG index (>0.6) were detected in 11/14 (79%), while pleocytosis (>5 white blood cells) was reported in 3/9 (33%; median cell number, 22,5 [range, 20–25]). In those with relapsing-remitting course, the median relapse number was 3,5 (range, 1–27), with a median EDSS at attack nadir of 4 (range, 1–5). The median follow-up was 4 years (range, 2 months-20 years).

MOG-IgG positivity

Ten patients underwent >1 test (median, 2 [range, 2–7]). The initial result was negative in 3/10 (30%). In those with available timing of testing, the frequency of MOG-IgG positivity was not significantly different during attacks (5/9 [56%]) vs remission (7/8 [88%]); $p=0.3$ (Fisher's exact test). All tests except two were performed during/after immunosuppressive/modulating treatment. In 7 patients, MOG-IgG positivity was detected during the progressive phase of the disease.

Treatment response and outcomes

Disease relapses were treated with high-dose corticosteroids in all, with addition of plasmapheresis and/or intravenous immunoglobulins in 2. Of 10 patients with relapsing-remitting disease who underwent maintenance immune-suppression/modulation, 7 (70%) relapsed on glatiramer acetate, interferon, azathioprine, dimethyl fumarate, or oral steroids; no relapses were observed under fingolimod, natalizumab, alemtuzumab, or rituximab/ocrelizumab. None of those with progressive disease improved with treatment.

Discussion

Patients with typical MS lesions on MRI and MOG-IgG positivity did not differ from what expected in seronegative patients with a definite MS diagnosis in attack severity, treatment response, MRI lesion evolution over time, and outcomes. False positive results for MOG-IgG are more likely than atypical manifestations of the MOGAD spectrum in these patients, that should reasonably be managed as MS patients. A correct interpretation of MOG-IgG positivity based on the accompanying clinical-MRI phenotype is crucial as misdiagnosis may result in incorrect treatment.

During the last decade, the characteristic clinical-MRI phenotype of MOGAD has been delineated, allowing distinction from other CNS demyelinating disorders.[1–3] MOGAD features that are generally not observed in MS include absence of CSF-restricted oligoclonal bands, CSF pleocytosis with >50 white blood cells, and severe attacks often followed by complete/nearly complete recovery with lack of secondary progression.[1,2,8] Serial MRIs in MOGAD show resolution of T2-abnormalities in 50–70% of cases and rare occurrence of new asymptomatic lesions, in contrast to MS where T2-lesions typically persist and increase in number over years, suggesting a different pathophysiology.[9,10] In this study, all included patients showed clinical-MRI characteristics typical of MS both during attacks (*e.g.* moderate attack severity with EDSS ≤ 5) and at follow-up (*e.g.* response to high-efficacy MS-targeted agents, MRI lesion persistence/accumulation, disease progression). The detection of CSF-restricted oligoclonal bands in nearly 80% of patients, in particular, represent a major red flag and strongly argues against a MOGAD diagnosis.

Despite the high specificity of live cell-based assays, MOG-IgG testing in large unselected populations may lead to false positive results given the rarity of MOGAD compared to other disorders.[4] This is especially relevant when the test is performed indiscriminately in patients with MS phenotypes, as MOGAD is 40–50 times less common than MS.[2,4] In a recent series of 1260 patients consecutively tested for

Table 1. Clinical-laboratory characteristics and treatment response in 16 identified cases with MOG-IgG positivity ant typical MS lesions on MRI.

Author (year)	Age/ sex	Highest MOG-IgG titer (cut-off)* and type of assay	Disease course (n. of attacks)	CSF findings	Acute treatments	Maintenance treatments	Relapses during treatment	Worst EDSS	Follow-up duration
Spadaro et al. (2016) 1st case	27/ F	Titre NA, FACS	RR (27)	OCB +	IVMP, IVIg, PLEX	IFN, GA, MTX, RTX	Several relapses, stabilized on RTX	5	18 years
Spadaro et al. (2016) 4th case	57/ F	Titre NA, FACS	RR (8)	OCB +	IVMP	IFN, GA	Several relapses	4	20 years
Spadaro et al. (2016) 5th case	36/ M	Titre NA, FACS	RR (5)	OCB +	IVMP, PLEX	IFN, NAT, RX	Relapsed under IFN, stabilized on NAT	4	14 years
Perotin et al. (2018)	39/ M	1:320 (NA), LCBA	SPMS (2)	OCB +	IVMP	IFN, GA, MTX, RTX (all during disease progression)	New asymptomatic lesions on MRI	7.5	20 years
Breza et al. (2019)	31/ M	1. 1:80 (1:20), LCBA; 2. 1:360 (1:160), LCBA; 3. > 1:10, FCBA	RR (2)	OCB +; IgG Index: 1.16	IVMP, OS	OS	Possible clinical relapse during steroid taper	1	2 months
Pawlitzki et al. (2020)	35/ NA	Titre NA, positivity confirmed by 2 different LCBA and 1 FCBA	RR (2)	WBC: 25; OCB +	IVMP	IFN for 6 months switched to GA for 14 months	No	1	3 years
Otto et al. (2020)	34/ F	1:640 (1:160), LCBA	RR (1)	OCB +; high IgG Index	IVMP	Alemtuzumab	No	3.5	4,5 years
Dolbec et al. (2020)	42/ F	1:40 (NA), LCBA	RR (2)	OCB +; IgG index: 0.62	IVMP	IFN discontinued due to poor tolerance; RTX	No	3	18 years
Takahashi et al. (2021) 1st case	27/ F	1:256 (1:128), LCBA	RR (4)	OCB-; IgG Index: 0.91	IVMP	FTY for 2.5 years, switched to DMF before pregnancy; OS	Relapse on DMF, after FTY discontinuation	5	4 years
Takahashi et al. (2021) 2nd case	27/ F	1:256 (1:128), LCBA	RR (6)	WBC: 20; OCB +;	IVMP	IFN, FTY for 1 year switched to	Relapses on IFN	2	4 years

(continued)

Table 1. Continued.

Author (year)	Age/ sex	Highest MOG-IgG titer (cut-off)* and type of assay	Disease course (n. of attacks)	CSF findings	Acute treatments	Maintenance treatments	Relapses during treatment	Worst EDSS	Follow-up duration
				IgG Index: 2.06		DMF due to adverse events	and after FTY discontinuation		
Marcucci et al. (2021) 1st case	54/ M	1:100 (1:20), FACS	PPMS	WBC: high; OCB–	–	OCR	Stabilized	NA	1-1,5 years
Marcucci et al. (2021) 2nd case	58/ F	1:100 (1:20), FACS	PPMS	OCB +	–	OCR	Progressed	NA	1-1,5 years
Marcucci et al. (2021) 3rd case	65/ M	1:40 (1:20), FACS	PPMS	OCB-	–	No	NA	NA	8 months
Marcucci et al. (2021) 4th case	66/ F	1:40 (1:20), FACS	PPMS	NA	–	Monthly IVIg	Stabilized	NA	1-1,5 years
Marcucci et al. (2021) 5th case	48/ M	1:20 (1:20), FACS	PPMS	NA	–	DMF, Monthly IVIG	Progressed on DMF, stabilized on monthly IVIG	NA	1-1,5 years
Yang Zheng et al. (2021)	25/ F	1:32 (NA), FCBA	RR (3)	OCB + ; IgG index: 0.54	IVMP	AZA, RX	Relapsed under AZA, stabilized on RX	4,5	2 years

Abbreviations: AZA, azathioprine; CBA, cell based assay; DMF, dimethyl fumarate; EDSS, expanded disability status scale; FTY, fingolimod; GA, glatiramer acetate; INF, interferon; IVCS, intravenous corticosteroids; IVIg, intravenous immunoglobulin; IVMP, intravenous Methylprednisolone; MBP, myelin basic protein; MITOX, mitoxantrone; MP, methylprednisolone; NA, not available; NAT, natalizumab; OCB, oligoclonal bands; OCR, ocrelizumab; OS, oral steroids; PLEX, plasma exchange; PPMS, primary progressive multiple sclerosis; RR, relapsing remitting; RX, rituximab; SPMS, secondary progressive multiple sclerosis; WBC, white blood cells.
*MOG-IgG testing was performed by visual assessment on cell-based assays using live (LCBA) or fixed (FCBA) transfected cells, or by fluorescence activating cell sorting (FACS); 2 patients tested positive with >1 assay.

MOG-IgG, 26/92 (28%) patients with a positive result had an alternative diagnosis, including typical MS, genetically (*e.g.* adrenomyeloneuropathy) or pathologically (*e.g.* neoplasms) confirmed diagnoses, showing false positives may occur across different neurologic disorders.[4] Similarly, rare patients with coexisting positivity for AQP4-IgG and MOG-IgG have a clinical-MRI phenotype more consistent with AQP4-IgG-NMOSD than MOGAD.[11]

Patients with false MOG-IgG positivity typically have low antibody titers, similar to the reported titers in this report (within 3 serial dilutions from the reported positivity cut-off; Table 1).[4] Three patients initially tested negative for MOG-IgG, suggesting repeated testing in the same patients may increase the likelihood of false positivity. On the contrary, testing during different disease phases (attack, remission, or progression) do not seem to alter the probability of obtaining a false positive result. The detection of false MOG-IgG positivity in these patients might be related to the use of less specific laboratory assays (*e.g.* fixed vs live cell-based assays), cross reactivity, and/or fluctuations of low MOG-IgG titers across different positivity cut-offs. In the latter case, MOG-IgG detection would rather represent a "true" positive, although clinically irrelevant, test result.[12]

Limitations of this study include its retrospective nature and small sample size. The MRI features of MOGAD and MS may sometimes overlap making distinction challenging (*e.g.* tumefactive MS lesions), and MOGAD lesions may fulfill MS MRI criteria for dissemination in time and space but they generally have different characteristics and we focused on cases in whom all presented MRI features were suggestive of MS. Efficacy comparisons between different immunosuppressive/modulating drugs were limited by the small sample size. Certain drugs are effective for both MOGAD and MS (*e.g.* rituximab) and might represent a reasonable treatment option when a false MOG-IgG positivity is suspected.

Declaration of Conflicting Interests

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Supplemental material

Supplemental material for this article is available online.

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