

Relapsing optic neuritis and isolated transverse myelitis are the predominant clinical phenotypes for patients with antibodies to myelin oligodendrocyte glycoprotein in India

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Abstract

Background: Clinical phenotypes of patients with antibodies to myelin oligodendrocyte glycoprotein (anti-MOG+) are unknown in India.

Objectives: Retrospectively to characterise anti-MOG+ patients with inflammatory central nervous system disorders in India.

Method: A total of 87 patients with non-multiple sclerosis demyelinating disorders (excluding acute disseminated encephalomyelitis) who were seronegative for anti-aquaporin 4 antibody were retrospectively analysed using a cell-based assay for anti-MOG+ status.

Results: Twenty-five patients were anti-MOG+ in this cohort. They represented 28.7% (25/87) of patients who tested negative for anti-AQP4+. Sixty-four per cent (16/25) of anti-MOG+ patients were men and had a relapsing course. Patients with recurrent optic neuritis and those with a single attack of acute longitudinally extensive transverse myelitis were the most common phenotypes.

Conclusion: Relapsing optic neuritis was the most common phenotype, contrasting with a lower risk of relapses in transverse myelitis.

Keywords: Optic neuritis, myelitis, myelin oligodendrocyte glycoprotein antibody, aquaporin-4 antibody, India

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Introduction

A significant proportion of non-Caucasian patients with idiopathic inflammatory disorders have atypical features for multiple sclerosis (MS). Among these, patients with autoantibodies against myelin oligodendrocyte glycoprotein (anti-MOG+) have been described in those who were negative for aquaporin-4 antibodies (anti-AQP4).^{1–7} In this study we describe the frequency and clinical characteristics of anti-MOG+ patients among Indian patients.

Patients and methods

All patients were obtained from the Mangalore demyelinating disease registry that has prospectively enrolled all consecutive patients with central nervous system (CNS) demyelinating disorders on the

southwestern coast of India. The inclusion criteria for this study were as follows: (1) a clinical diagnosis of ‘non-MS’ CNS inflammatory demyelinating disorders including monophasic and recurrent disorders; (2) seronegative status for AQP4+ by live cell-based assay. Patients presenting with acute disseminated encephalomyelitis (ADEM) were not included. Anti-AQP4 and anti-MOG cell-based assay was blindly performed at Tohoku University using live transfected HEK-293 cells with AQP4-M23 isoform and full-length MOG as described previously.³ All patients had blood draws during an attack and prior to initiating parenteral steroids. In 64% of patients with relapsing disease the samples were obtained during the first relapse. Clinical and magnetic resonance imaging (MRI) data were reviewed

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retrospectively. This study was approved by the institutional ethics committee and all patients signed an informed consent form.

Results

Eighty-seven patients seen between January 2011 and December 2015 who were seronegative for anti-AQP4+ cell-based assay were included. Twenty-five patients (28.7%) tested positive for anti-MOG+. These included 11 (44%) recurrent optic neuritis (RON), nine (36%) single attack of longitudinally extensive transverse myelitis (LETM), three (12%) recurrent LETM and two (8%) neuromyelitis optica (NMO) patients (Wingerchuck, 2006).⁸ Sixty-four per cent (16/25) of anti-MOG+ patients were men and had a relapsing course. The mean age of disease onset in the group as a whole was 24.4±12.8 SD (median age 24 years, range 5–55). There was no significant difference in the age of disease onset between various subgroups: those presenting with RON versus myelitis. The duration of illness was 5.7±3.90 years (median 4 years, range 1–16). We identified a single patient who developed symptoms after 3 months postpartum. The initial attack was LETM in 56% (14/25) and optic neuritis in the remainder. Bilateral simultaneous optic neuritis was seen in one patient. One patient had Lhermitte's sign heralding the relapse. At last follow-up, Kurtzke's Expanded Disability Scale (EDSS) showed a median visual functional score of 0 (range 0–5) and a disability score of 1 (range 0–10). One patient (Table 1; patient 1) died. He was 48 years old at the time and had unilateral blindness and paraplegia after recurrent optic neuritis and myelitis. He died from complications related to uncontrolled urinary tract infection.

Anti-MOG antibody negative patients ($n=62$) included isolated LETM 45.2% (28/62), NMO 27.4% (17/62), RON 17.7% (11/62) and recurrent LETM 9.7% (6/62). Seronegative patients had a similar age of onset of disease as anti-MOG+ patients (see Supplementary Tables 1 and 2), no gender predilection and had greater disability. The latter may be accounted for by the high number of patients with LETM in this group.

Unilateral or bilateral thickening of the optic nerve with T2 weighted (T2W) hyperintense signals and/or patchy enhancement was seen in 61.5% (8/13) of anti-MOG+ patients. Optic chiasm was partially involved (Figure 1(a–c)) in 15.4% (2/13). The dorsal cord was involved in 57.1% (8/14) of patients (Figure 1(d)) presenting with long segment myelitis.

In the remainder, cervical cord lesions remained contained and did not extend into the cervicomedullary or caudal brainstem regions. Axial sections showed involvement of the central part of the cord in 64.3% (9/14) who had myelitis. The most common abnormality on brain MRI was subcortical white matter lesions (atypical for MS), which was seen in 24% (6/25) of patients (Figure 1(e and f)). Two patients (8%) with brain lesions had altered sensorium and headache at onset. There were no striking differences in imaging between anti-MOG+ and seronegative patients.

In this retrospective analysis, all relapsing anti-MOG+ patients had been treated with immunosuppressant therapy (Table 1). Two patients with anti-MOG+ RON remained free of new attacks after discontinuation of immunosuppressants (median follow-up of 22 months). Three patients with RON received steroids during relapses but they did not take long-term immunosuppressants (Table 1; patients 17, 20, 25). One patient had been treated elsewhere initially with beta-interferon for 12 months, with clinical worsening.

Discussion

We identified a significant subgroup of patients (28.7%) with anti-MOG+ among patients with idiopathic inflammatory CNS disorders who were negative for anti-AQP4+. Relapsing optic neuritis was the most common phenotype and has been reported previously.^{9,10} But patients with a single attack of LETM affecting the dorsal cord were also frequent. The reason for a higher risk of relapses in patients with optic neuritis is unknown. Further prospective longitudinal studies may clarify whether those patients maintain anti-MOG+ for long periods. These patients shared some clinical similarities with anti-AQP4+ NMO spectrum disorders with limited phenotypes such as RON and LETM. NMO, satisfying Wingerchuck, 2006 criteria⁸ was seen in two patients only (cases 1 and 2, Table 1). Symptomatic brainstem lesions causing nausea, vomiting and hiccups were uncommon. Thus the majority of patients did not fulfill the new diagnostic criteria for NMO spectrum disorders.¹¹

The visual and disability outcome in our cohort after more than 5 years of disease was good in the majority of patients, but anti-MOG+ disease may occasionally be very severe as was evident in one of our patients. The MRI of the spinal cord showed a predilection for dorsal cord involvement and a lack of cranial extension of cervical cord lesions into the brainstem commonly seen in anti-AQP4+ NMO

Table 1. Anti-MOG+ patients – clinical course, MRI and therapy.

No.	Diagnosis	Age at onset	Gender	Disease duration	VFS	EDSS	Relapse prevention therapy	Brain MRI lesions	Optic nerve +	MRI spinal cord
1	NMO	46	M	8	5	10	AZA for 1 year prior to death	Subcortical	Unilateral	C5–D7 cord atrophy
2	NMO	24	F	6	2	1.5	AZA	Normal	Bilateral & chiasm	D1–D6
3	RTM	6	M	4	0	2	MMF	Periaqueductal	Normal	D1–D8
4	RTM	21	F	2	0	2	IFN (6 months), MMF	Subcortical	Normal	C4–D7
5	RTM	5	M	14	0	1	NT	Brainstem & thalamus	Normal	D7–conus
6	ATM	31	M	8	0	0	NT	Normal	Normal	D1–D6
7	ATM	55	M	6	0	0	NT	Normal	Normal	D5–D7
8	ATM	26	M	5	0	1	NT	Brainstem	Normal	C4–D7
9	ATM	26	M	4	0	0	NT	Normal	Normal	D4–D9
10	ATM	22	M	3	0	0	NT	Normal	Normal	C3–conus
11	ATM	37	M	2	0	0	NT	Normal	Normal	D1–D6
12	ATM	42	M	1	0	1	NT	Normal	Normal	D6–D9
13	ATM	16	F	1	0	1	NT	Subcortical	Normal	C2–T6
14	ATM	14	M	3	0	0	NT	Thalamus, brainstem, subcortical	Normal	C6–D8
15	RON	14	M	16	4	2	NT	Normal	Unilateral	Normal
16	RON	28	M	8	2	1	MMF	Normal	Normal	Normal
17	RON	28	F	4	2	1	NT except steroids during relapse	Normal	Normal	Normal
18	RON	16	M	4	1	1	Stopped AZT after 1 year, no recurrence	Normal	Unilateral	Normal
19	RON	32	F	12	2	1	Stopped AZT after 1 year, no recurrence	Normal	Unilateral	Normal
20	RON	19	F	10	1	0	NT except steroids during relapse	Normal	Unilateral	Normal
21	RON	5	F	8	2	1	MMF	Normal	Normal	Normal
22	RON	28	M	2	2	1	MMF	Normal	Bilateral optic nerve & chiasm	Normal
23	RON	7	F	4	1	0	MMF	Subcortical	Normal	Normal
24	RON	41	M	3	2	1	MMF	Normal	Unilateral	Normal
25	RON	20	F	4	0	0	NT except steroids during relapse	Thalamus, brainstem, subcortical	Normal	Normal

anti-MOG+; autoantibodies against myelin oligodendrocyte glycoprotein; MRI: magnetic resonance imaging; NMO: neuromyelitis optica; RTM: recurrent transverse myelitis; ATM: acute transverse myelitis; RON: recurrent optic neuritis; AZA: azathioprine; MMF: mycophenolate mofetil; VFS: visual functional score; EDSS: Expanded Disability Status Scale; NT: not treated; NA: not applicable.

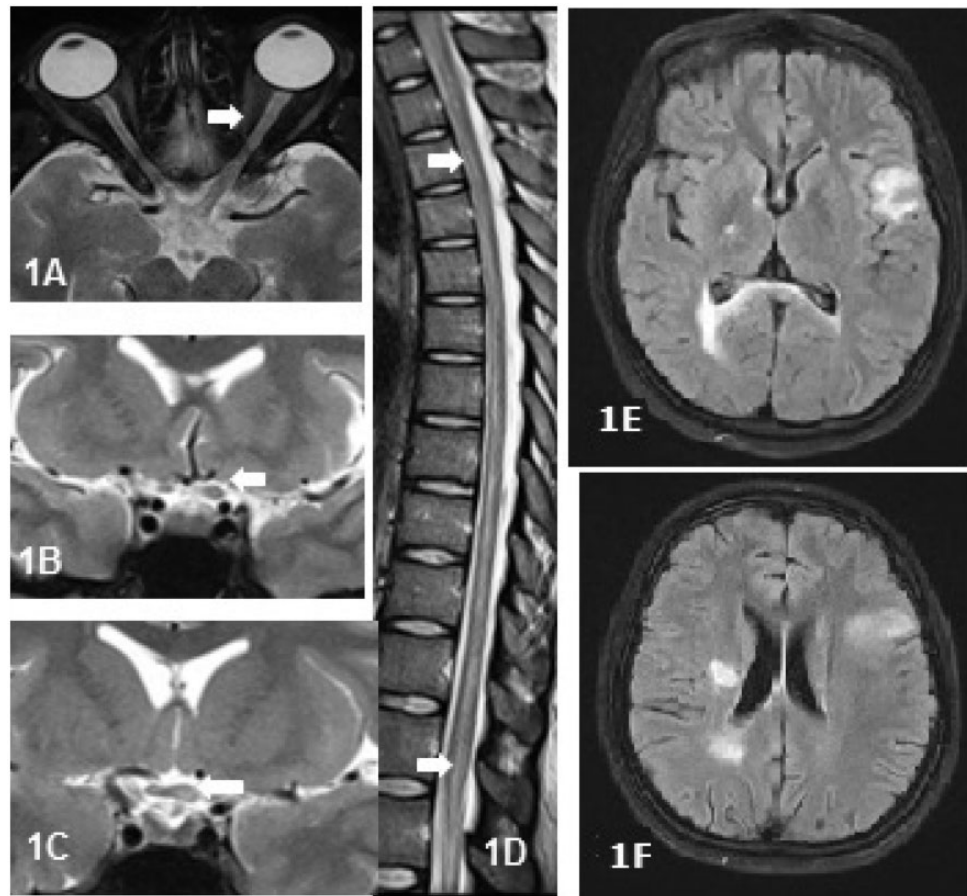


Figure 1. Magnetic resonance images of the spinal cord and optic nerve in anti-MOG+ patients. Fat suppressed (FATSAT) axial image of the orbit (a) and T2 weighted (T2W) coronal images in a 31-year-old woman with recurrent optic neuritis showing thickened and hyperintense intraorbital (a) and intracranial segment (b) of the left optic nerve with extension into the optic chiasm on the left side (c). (d) T2W sagittal image of the spinal cord showing hyperintense linear cord lesion extending from upper dorsal cord to the conus in a 21-year-old man with isolated transverse myelitis. (e) and (f) 25-Year-old woman with recurrent myelitis showing atypical brain lesions.

spectrum disorders. Bilateral simultaneous optic neuritis was uncommon in our cohort, but the orbital MRI showed bilateral long segment optic nerve involvement in those bilaterally affected with optic neuritis. Unlike other studies^{3,7,12} we found partial involvement of the optic chiasm on the orbital MRI of two patients with RON. First line disease-modifying drugs used for MS such as beta-interferon may worsen anti-MOG+ diseases as experienced by one of our patients. Several reports showed an increase in relapses, worsening of disability,¹³ and an increase in the NMO-IgG titre¹⁴ while on disease-modifying therapy with beta interferon. This may be due to a difference in immune pathogenesis between MS and antibody-mediated disorders such as anti-AQP4+ and anti-MOG + disorders.

Response to primary immunosuppressant therapy in our small cohort of relapsing anti-MOG+ patients was satisfactory, with none of our treatment-compliant patients experiencing breakthrough relapses.

In conclusion, almost a third of our cohort of patients from India with non-MS demyelinating disorders and negative for anti-AQP4+ had anti-MOG positivity. Relapsing optic neuritis was the most common phenotype, contrasting with those patients who had a single attack of LETM. Long-term immunosuppressive therapy may benefit those patients with a relapsing disease course. A significant number of patients in our cohort were seronegative underscoring the heterogeneity in aetiopathogenesis of these disorders. A prospective study that includes a larger

cohort and a wider spectrum of disorders such as MS and ADEM may overcome some of the limitations of this study.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Lekha Pandit, Sharik Mustafa, Anitha D'Cunha, Chaithra Malli, Akshatha Sudhir and Toshiyuki Takahashi. Dr Sato has received speaker honoraria from Novartis. Dr Fujihara serves on scientific advisory boards for Bayer Schering Pharma, Biogen Idec, Mitsubishi Tanabe Pharma Corporation, Novartis Pharma, Chugai Pharmaceutical, Ono Pharmaceutical, Nihon Pharmaceutical, Merck Serono, Alexion Pharmaceuticals, Medimmune and Medical Review; has received funding for travel and speaker honoraria from Bayer Schering Pharma, Biogen Idec, Eisai Inc., Mitsubishi Tanabe Pharma Corporation, Novartis Pharma, Astellas Pharma Inc., Takeda Pharmaceutical Company Limited, Asahi Kasei Medical Co., Daiichi Sankyo, and Nihon Pharmaceutical; serves as an editorial board member of *Clinical and Experimental Neuroimmunology* (2009 to present) and an advisory board member of the *Sri Lanka Journal of Neurology*; has received research support from Bayer Schering Pharma, Biogen Idec Japan, Asahi Kasei Medical, The Chemo-Sero-Therapeutic Research Institute, Teva Pharmaceutical, Mitsubishi Tanabe Pharma, Teijin Pharma, Chugai Pharmaceutical, Ono Pharmaceutical, Nihon Pharmaceutical, and Genzyme Japan.

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