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ORIGINAL COMMUNICATION

Usefulness of MOG-antibody titres at first episode to predict the future clinical course in adults

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Abstract

Objective To analyze whether myelin oligodendrocyte glycoprotein antibody (MOG-Ab) titres at onset of the disease were different according to the clinical phenotype at presentation, and to investigate whether the titres were associated with risk of further relapses or predicted clinical outcome in adult patients. Finally, we assessed an alternative method to the classical measurement of MOG-Ab levels by serial dilutions.

Methods This is a retrospective study including 79 MOG-Ab-positive adult patients, whose samples were obtained at first episode. MOG-Ab were tested by cell-based assay. HEK293 cells were transfected (tHEK293) with human-MOG plasmid. Non-tHEK293 cells were used as negative controls. Assessment of antibody titres was performed by serial dilution, and delta mean fluorescence intensity ratio signal (MOG-ratio ΔMFI) by flow cytometry. MOG-ratio ΔMFI was calculated as follows: (MFI tHEK293cells- MFI non-tHEK293cells)/MFI non-tHEK293cells. MOG-ratio ΔMFI was calculated from the first serum dilution at 1:320. The association between MOG-Ab titres and risk of relapse was analyzed by Cox regression. The association between MOG-Ab titres and visual or motor disability at last follow-up was performed by binary logistic regression. Poor visual outcome was defined when patients displayed some degree of visual disability (visual acuity [VA] < 20/20) and poor motor outcome when patients displayed some degree of motor disability (Disability Status Scale [DSS] > 1). We also investigated correlations between MOG-Ab titres and MOG-ratio ΔMFI.

Results MOG-Ab titres were higher in Caucasians than in those with other ethnicities, and in patients with a more severe VA (VA ≤ 20/100) or motor disability (DSS ≥ 3.0) at onset ($p = 0.006$, 0.034, and 0.058, respectively). MOG-Ab titres were not associated with risk of relapses or with the final clinical outcome. MOG-ratio ΔMFI correlated with MOG-Ab titres in the whole cohort ($\rho = 0.90$; $p < 0.001$), and when stratified by initial clinical phenotype.

Conclusion High MOG-Ab titres at onset are associated with a more severe presentation, but do not predict the future disease course. MOG-ratio ΔMFI is an alternative and straightforward method to determine MOG-Ab levels.

Keywords MOG antibodies · Titre · Prognosis · Neuromyelitis optica · Optic neuritis · Myelitis

Introduction

Myelin oligodendrocyte glycoprotein antibodies (MOG-Ab) have been mainly described in young patients with acquired demyelinating syndromes (ADS) with different clinical presentations, mostly optic nerve attacks, and a good prognosis in general [1–4]. However, up to 45% of patients relapse within the first 2 years after onset, leading to visual or motor irreversible disability in up to 16% and 25%, respectively [3, 4]. Up to now, there is no consensus regarding treatment

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strategies to prevent relapses or disability after a first episode in MOG-Ab-associated disease. Thus, there is a need to identify patients that could benefit from a more aggressive acute treatment or maintenance immunotherapy at the beginning of the disease. In this regard, we consider MOG-Ab titres at the onset of disease as a potential baseline biomarker to predict the clinical course in such patients.

Some studies including mixed populations (pediatric and adults) have found that certain clinical phenotypes characterized by a widespread demyelination (i.e., acute disseminated encephalomyelitis [ADEM]) could be related to higher MOG-Ab titres at onset of symptoms [5–7]. Furthermore, some of them have shown higher MOG-Ab titres at relapse compared to the remission phase of the disease,[4, 5, 8] and an association between the persistence of MOG-Ab over time and the risk of a relapsing course in contrast to monophasic forms [3, 9, 10]. Nonetheless, whether MOG-Ab titres at first episode are associated with a specific clinical phenotype or are useful to predict both future relapses and outcome in adults with MOG-Ab-associated disease is currently unclear.

The aim of the present study was to analyze in adult patients with MOG-Ab-associated disease whether MOG-Ab titres at onset of the disease were different according to the clinical phenotype at presentation, and to investigate whether the titres were associated with a risk of further relapses or predictive of the outcome. Finally, we assessed an alternative method to the classical measurement of MOG-Ab levels by serial dilutions.

Methods

Patients

We retrospectively recruited patients from French and Spanish referral centers for neuro-inflammatory disorders from January 2014 to January 2018, who fulfilled the following criteria: (1) aged ≥ 18 years at onset; (2) diagnosis of ADS, defined as an acute clinical demyelinating episode of the central nervous system (CNS) persisting for a minimum of 24 h; (3) the presence of MOG-Ab in a serum sample obtained within 3 months from onset of the disease, defined as the first clinical episode of the disease; (4) ≥ 6 months of follow-up from onset of the disease.

French and Spanish patients were selected within the scope of the *Observatoire Français de la Sclérose en Plaques* (OFSEP), and *Red Española de Esclerosis Múltiple* (REEM), respectively.

Data included demographics (sex, ethnicity [Caucasian, African, Asian, Hispanic, Afro-American], and age at onset of the disease) and clinical features such as phenotype at onset and at last follow-up, number of relapses and time to the first relapse.

Visual disability was measured by the visual functional system and reported as visual acuity (VA), and motor disability by the Disability Status Scale (DSS), both at onset and last follow-up [4]. Acute treatment (intravenous [i.v] methylprednisone, i.v. immunoglobulins or plasma exchanges) and the initiation of maintenance therapy within the first 3 months from the first episode (immunosuppressants [rituximab, azathioprine, mycophenolate mofetil, mitoxantrone, cyclophosphamide or methotrexate], multiple sclerosis (MS) disease-modifying drugs, or low-dose corticosteroids for at least 6 months) were noted. Choice of treating was based upon neurologists' choice regardless of MOG-Ab titres at first episode.

Disability at onset was considered severe when VA ≤ 20/100 or DSS ≥ 3.0 at onset of disease for visual and motor symptoms, respectively. To evaluate the outcome, patients were categorized into two groups. Visual disability was evaluated only in patients with an initial optic neuritis (ON) at onset; we defined good visual outcome when patients did not display visual disability (VA = 20/20), and poor visual outcome when patients displayed some degree of visual disability (VA < 20/20), both at last follow-up. Motor disability was evaluated in patients with a non-ON phenotype at onset; we defined good motor outcome when patients did not display motor disability (DSS ≤ 1.0), and poor motor outcome when patients displayed some degree of motor disability (DSS > 1), both at last follow-up.Patients were classified in the following categories at last follow-up: isolated ON or myelitis (i.e., monophasic or relapsing transverse myelitis [TM] or ON), neuromyelitis optica spectrum disorders (NMOSD) [11], ADEM [12], and MS [13]. Patients with short TM and ON who did not strictly fulfill NMOSD criteria were classified as optico-spinal phenotype [11].

Clinical diagnosis was supported by magnetic resonance imaging (MRI) studies obtained at the discretion of the treating clinician at onset and during the follow-up as part of the routine clinical practice. T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and T1-weighted post-contrast sequences were performed.

The study was approved by the ethics committee of the University Hospital of Lyon, France, and Hospital Clinic of Barcelona, Spain. All patients gave their informed consent to participate in the study.

Cell-based assays

MOG-Ab were analysed by cell-based assay (CBA) in the Neuroscience Research Centre of Lyon [14]. Briefly, HEK293 cells were transfected (tHEK293) with pEGFP-N1-hMOG plasmid (kind gift from Markus Reindl, Innsbruck, Austria) for 48 h, and then incubated with patient's

serum. Bound IgG was detected with a fluorescent secondary antibody, APC-Goat anti human IgG-Fcγ fragment specific (1:100 dilution, Jackson ImmunoResearch). Non-tHEK293cells were used as negative controls. Evaluation of signal intensity was performed by flow cytometry.

Quantitative assessment of MOG-Ab was performed either by titration or by evaluation of the delta mean fluorescence intensity ratio signal (MOG-ratio ΔMFI). Titration of positive samples was performed by serial dilution until loss of positive signal (from 1:320 to 1:40.960). MOG-ratio ΔMFI was calculated as follows: (MFI tHEK293cells-MFI non-tHEK293cells)/MFI non-tHEK293cells. MOG-ratio ΔMFI was calculated from the first serum dilution at 1:320 (Supplementary Fig. 1).

Aquaporin4 (AQP4)-Ab were assessed by live CBA in the Neuroscience Research Centre of Lyon, and in the Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS) of Barcelona, as reported [15, 16].

Statistical analysis

MOG-Ab titres were treated as a continuous variable but also categorized as low (≤ 1/1280), intermediate (1/2.560–1/5.120), and high (≥ 1/10.240) levels.

To study the association between clinical phenotypes and MOG-Ab titres, non-parametric tests were used (Spearman correlations for continuous variables, Mann–Whitney *U* test when comparing two groups, and Kruskal–Wallis test when comparing more than two groups).

We performed two different analyses to evaluate the prognostic value of MOG-Ab titres at onset. First, to evaluate time to first relapse, a univariate Cox proportional hazard model was used according to baseline variables, and categorical MOG-Ab levels. These results were expressed as hazard ratios (HR) with 95% confidence intervals (95% CI). Second, to evaluate good vs. poor visual or motor outcome at last follow-up, univariate binary logistic regression was used. Results were expressed as odds ratio (OR) with 95%CI. Variables from each model with a p value ≤ 0.20 were included in the Cox and binary logistic regression multivariate model, respectively.

To correlate MOG-Ab titres with MOG-ratio ΔMFI (treated as a continuous variable), the Spearman test was used both in the whole cohort, and stratified by clinical phenotype at onset.

All statistical analyses were performed using STATA-12 (64-bits) software and GraphPad Prism (version 5.0), and a $p < 0.05$ was considered significant.

Data availability

This study was done within the framework of OFSEP. While anonymization techniques might result in impoverishment of data (Article 29 of Directive 95/46/EC, Opinion 05/2014 on Anonymisation Techniques—0829/14/EN WP 216), data used for this study were only pseudonymized. However, access to OFSEP data to conduct a scientific project is possible by following the OFSEP data access process (ofsep.org/en/ data-access), respecting French law.

Results

Cohort description and MOG-Ab titres according to baseline patient characteristics

Seventy-nine MOG-Ab-positive adult patients fulfilled the required criteria and were included. Among them, 45 (57%) were female, median age at onset was 38.7 years [interquartile range (IQR) 29.6–50.7], and 74 (93.7%) were Caucasians. MOG-Ab titres were higher in Caucasian [median, IQR; 5120 (5120–40,960), than in non-Caucasian patients (2560 (1280–2560))], $p = 0.006$ (Table 1; Supplementary Table 1). Median time from the first episode to antibody sampling was 19 days (IQR 8–52).

At onset, 48 (60.8%), and 19 (25.1%) of the patients presented isolated ON and myelitis, respectively. Simultaneous ON and myelitis was observed in eight patients (10.1%), and encephalopathic/brainstem syndromes in four (5.1%) (Table 1). After a median follow-up of 19.0 months (range, 6.5-155.9), 29 (36.7%) patients presented at least one relapse.

Clinical diagnoses at last follow-up were isolated ON in 44 (55.7%) patients, and isolated myelitis in 16 (20.3%). NMOSD was observed in 12 (15.2%) patients, ADEM in 5 (6.3%), and MS or optico-spinal cord phenotype in 1 (1.3%) patient each. No association was found between MOG-Ab titres and clinical phenotype at onset (Table 1, and Supplementary Fig. 2.a), or at last follow-up (Supplementary Table 2, and Supplementary Fig. 2.b).

Patients with a more severe visual disability at onset displayed higher MOG-Ab titres [median, IQR 5120 (5120–40,960)] than patients with mild visual disability [5120 (2560–20,480)], $p = 0.043$. Similarly, patients with a more severe motor disability at onset (DSS ≥ 3.0) had higher MOG-Ab titres [median, IQR 5120 (2560–40,960)] than those with mild motor disability [1280 (1280–1280)], $p = 0.058$ (Table 1). Nonetheless, titres were not significantly different between patients with normal (DSS < 4.0) [median, IQR 2560 (1920–1940,960)] and limited walking (DSS ≥ 4.0) [median 5120 (2560–10,240)] at onset, $p = 0.711$. In the same line, MOG-Ab titres were not related to recovery from the first attack neither among patients with an initial non-ON phenotype [OR 1.10 (95 CI% 0.99–1.01); $p = 0.981$] nor among patients with an initial ON phenotype [OR 0.99 (95 CI% 0.99–1.01); $p = 0.103$].

Table 1 Baseline demographic and clinical features associated with MOG-Ab titres at first episode

Baseline variables	MOG-Ab cohort, $n=79$	MOG-Ab titres, median (IQR)	p value[a]
Age at onset, years, median (range)	38.7 (18–73.1)	–	0.140[b]
18–29	22 (27.9)	5120 (2560–20,480)	0.131
30–49	36 (45.6)	5120 (2560–20,480)	
≥ 50	21 (26.6)	10,240 (5120–40,960)	
Females/male, *n* (%)	45 (57)/34 (43)	5120 (2560–40,960)/5120 (2560–40,960)	0.412
Caucasian/others, *n* (%)	74 (93.7)/5 (6.3)	5120 (5120–40,960)/2560 (1280–2560)	**0.006**
Clinical phenotype at onset, *n* (%)			
ON	48 (60.8)	7680 (5120–40,960)	0.465
Myelitis	19 (24.1)	5120 (2560–40,960)	
ON and myelitis	8 (10.1)	2560 (1920–1923,040)	
Encephalopathic/brainstem S.	4 (5.1)	5120 (3840–23,040)	
VA 20/100 at onset[c], *n* (%)			
20/100	16/43 (37.2)	5120 (2560–20,480)	**0.034**
≤ 20/100	27/43 (62.8)	5120 (5120–40,960)	
DSS at onset[d], *n* (%)			
0–2.5	2/31 (6.5)	1280 (1280–1280)	**0.058**
≥ 3.0	29/31 (93.6)	5120 (2560–40,960)	
Acute phase treatment (MTP/IgIV/PLEX), yes/no, *n* (%)	77 (97.5)/2 (2.5)	5120 (2560–40,960)/21,760 (2560–40,960)	0.823
Maintenance therapy[e], yes/no, *n* (%)	15 (19)/64 (81)	5120 (1280–40,960)/5120 (3840–40,960)	0.147

The values are given in bold when there is a significant difference ($p < 0.05$) or when there is a trend differences between groups ($p < 0.080$)

MOG-Ab myelin oligodendrocyte glycoproteins antibodies, *IQR* interquartile range, *y* years, *ON* optic neuritis, *EDSS* Expanded Disability Status Scale, *VA* visual acuity, *MTP* methylprednisolone, *IgIV* intravenous immunoglobulins, *PLEX* plasma exchange

[a] p values regarding MOG-Ab titres

[b]Spearman correlation was performed between continuous variables and MOG-Ab titres. Age at onset, $\rho=0.17$, $p=0.140$

[c]For visual disability (AV 20/100), only patients who presented with ON at first acute demyelinating syndrome and evaluated within 31 days from onset were included

[d]For motor disability comparison (DSS ≥ 3.0) patients who presented with non-ON phenotypes at first episode, and evaluated within 31 days from onset were included

[e]Maintenance therapy started within 3 months from the onset of disease. Only one patient started maintenance therapy before MOG-Ab titres sampling

Seventy seven out of 79 (97.5%) patients received treatment at the acute phase, and 15 (19%) started on maintenance therapy within the 3 months from the onset of disease (Table 1). Only one patient received maintenance therapy before MOG-Ab sampling.

When categorizing MOG-Ab in low, intermediate and high levels in the whole cohort, we also observed that patients with intermediate and high levels were mainly Caucasians, ($p=0.062$), and had a more severe visual, ($p=0.087$) and motor ($p=0.032$) disability at onset than patients with lower levels. Patient characteristics regarding categorized MOG-Ab levels are shown in Table 2.

Baseline characteristics associated with risk of relapse

MOG-Ab titres did not impact the risk of reaching a first relapse (Fig. 1a). An older age was associated with a lower risk of reaching a first relapse: HR of 0.39 (95 CI% 0.18–0.88; $p=0.023$) for patients aged 30–49 years, and 0.32 (95 CI% 0.12–0.92; $p=0.034$) for older than 50 years, with patients aged 18–29 years taken as a reference; Fig. 1b. The protective effect of age remained in the multivariate analysis: HR, 0.42 (95 CI% 0.19–0.95; $p=0.038$) for patients aged 30–49 years, and 0.33 (95% CI 0.11–0.95; $p=0.040$) for older than 50 years (Fig. 1c).

Baseline characteristics associated with good outcome at last follow-up

Among patients presenting an initial ON phenotype, 34/56 (60.7%) did not display visual disability after a median follow-up of 20.0 (range 6.5–155.9) months. No clinical, demographic baseline variables or MOG-Ab titres were associated with visual outcomes (Table 3).

Table 2 Demographic and clinical parameters associated with categorized serum MOG-Ab

	Categorical MOG-Ab titres			*p* value
	≤ 1280	2560–5120	≥ 10,240	
Number of patients	12	33	34	–
Age at onset, median (IQR), years	34.2 (29.0–39.0)	36.7 (29.8–48.1)	40.3 (29.6–53.5)	0.216
18–29	4 (33.3)	9 (27.3)	9 (26.5)	0.273
30–49	7 (58.3)	17 (51.5)	12 (35.3)	
≥ 50	1 (8.3)	7 (21.2)	13 (38.2)	
Females, *n* (%)	4 (33.3)	20 (60.6)	21 (61.8)	0.209
Caucasian, *n* (%)	10 (83.3)	30 (90.9)	34 (100)	**0.062**
Clinical phenotype at onset, *n* (%)				
ON	6 (50)	18 (54.6)	24 (70.6)	0.606
Myelitis	4 (33.3)	8 (24.2)	7 (20.6)	
ON and myelitis	2 (16.7)	4 (12.1)	2 (5.9)	
Encephalophatic/brainstem S.	0	3 (9.1)	1 (2.9)	
VA 20/100 at onset[a], *n* (%)				
20/100	5 (83.3)	5 (31.3)	7 (33.3)	**0.087**
≤ 20/100	1 (16.67)	11 (68.8)	14 (66.7)	
DSS at onset[b], *n* (%)				
0–2.5	2/6 (33.3)	0	0	**0.032**
≥ 3.0	4/6 (66.7)	15/15 (100)	10/10 (100)	

The values are given in bold when there is a significant difference ($p < 0.05$) or when there is a trend differences between groups ($p < 0.080$)

MOG-Ab myelin oligodendrocyte glycoproteins antibodies, *IQR* interquartile range, *y* years, *ON* optic neuritis, *DSS* Disability Status Scale, *VA* visual acuity

[a]For visual disability (AV 20/100), only patients who presented with ON at first acute demyelinating syndrome and evaluated within 31 days from onset were included

[b]For motor disability comparison (DSS ≥ 3.0) patients who presented with non-ON phenotypes at first episode, and evaluated within 31 days from onset were included

Among patients presenting an initial non-ON phenotype episode, 12/31 (38.7%) did not display motor disability after a median follow-up of 19.0 (range 6.9–155.9) months. The univariate analysis showed that younger patients were at higher risk for good outcome [OR 1.10 (95 CI% 1.02–1.21); $p = 0.020$], and the effect of the association was maintained in the multivariate analysis [OR 1.11 (1.01–1.22); $p = 0.025$]. MOG-Ab titres were not associated with motor outcome (Table 3).

MOG-ratio ΔMFI as an alternative method to measure MOG-Ab serum levels

Individual MOG-ratio ΔMFI highly correlated with MOG-Ab titres when analysed in the whole cohort regardless of the clinical phenotype, $\rho = 0.90$, $p < 0.001$ (Fig. 2.a). When the analysis was performed according to the clinical phenotype at onset, the correlations were as follows: ON $\rho = 0.91$ ($p < 0.001$), myelitis $\rho = 0.84$ ($p < 0.001$), encephalopathic/brainstem syndrome $\rho = 0.95$ ($p = 0.051$), and ON plus myelitis $\rho = 0.92$ ($p = 0.001$) (Fig. 2.b-e).

Discussion

The present study of adult patients with MOG-Ab-associated disease provides several observations of interest: (1) high antibody titres are associated with a more severe visual or motor disability at the first episode, but antibody titres do not discriminate the clinical phenotype; (2) MOG-Ab titres at first episode are not associated with risk of further relapses or with the final outcome; and (3) MOG-ratio ΔMFI obtained by flow cytometry is a useful alternative method to antibody titration for measuring serum MOG-Ab levels.

At onset, we found that patients with a more severe visual or motor disability displayed higher MOG-Ab titres than others. Higher titres have been recently described at the time of a relapse compared to remission periods [4, 5, 8]. This finding combined with our data supports the potential direct role of the antibody on the pathophysiology of MOG-Ab-associated disease. Indeed, MOG-Ab have been directly related to myelin damage at the acute phase of the disease with the remarkable increase of myelin basic protein (MBP) levels without elevation of glial fibrillary acidic protein (GFAP) in the CSF [17, 18]. Interestingly, we also

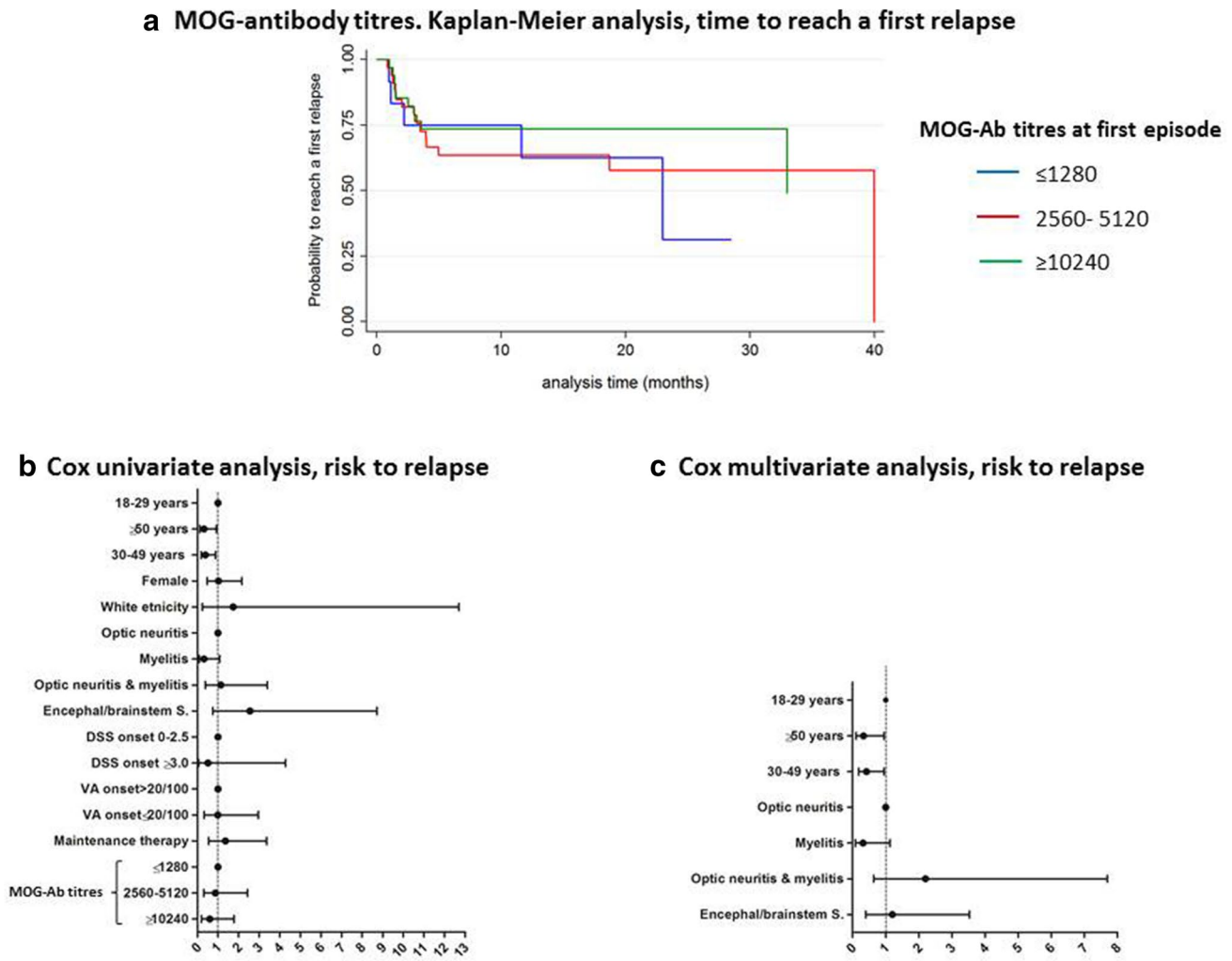

Fig. 1 Effect of basal variables on time to reach first relapse. **a** Time to reach a first relapse regarding categorized MOG-Ab titres; **b** Cox univariate analysis; **c** Cox multivariate analysis

found higher MOG-Ab titres in Caucasian compared to non-Caucasian patients. Although limited by the small number of non-Caucasian patients reported in the present study, this finding suggests an ethnicity-biased autoimmune susceptibility to MOG-Ab-associated disease that should be confirmed in further studies with larger sample size.

In the current cohort of adult patients, we could not find any association between MOG-Ab titres and a specific clinical phenotype at onset. A recent study mixing adults and pediatrics patients found higher MOG-Ab titres during episodes involving myelitis compared to non-myelitis but the inclusion criteria were different from our study as any episode during the course of the disease was considered [8]. In pediatric patients, an association between ADEM phenotype at onset and high MOG-Ab titres has been proposed by our group and others [5–7]. A possible explanation could be a more reactive immunity against MOG protein due to distinctive conformational features or continuous changes in myelin maturation during childhood [19, 20], leading to a more extensive demyelination presenting as an encephalopathic phenotype [21]. Accordingly, a more widespread inflammatory CNS involvement has also been reported in pediatric patients with AQP4-Ab-associated disease [22].

The early identification of potential markers to diagnose and predict the future clinical course could allow clinicians stratifying patients to different treatment strategies to eventually reduce relapse risk and long-term disability. Titres of different antibodies have been proved to be useful to predict clinical activity and prognosis in other autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis [23, 24]. Whether MOG-Ab titres at onset of disease predict disease course in adult patients with MOG-Ab-associated disease has not been evaluated so far. In pediatrics, there is only one study considering MOG-Ab titres at first episode as a valuable baseline biomarker. It included MOG-Ab-positive and -negative pediatrics with a first ADS and concluded that

Table 3 Effects of baseline variables and MOG-Ab titres on visual or motor outcome

	Good visual outcome		Good motor outcome	
	Univariate	Multivariate	Univariate	Multivariate
Age at onset, years	1.0 (0.97–1.04), 0.838		0.90 (0.83–0.98), **0.020**	0.90 (0.81–0.99), **0.025**
Females	1.27 (0.42–3.83), 0.672		1.71 (0.40–7.43), 0.471	
Caucasian ethnicity[a]	0.49 (0.05–5.05), 0.551		–	
Clinical phenotype at onset				
Optic neuritis/myelitis (ref)				
ON and myelitis	5.40 (0.62–47.70), 0.126	5.60 (0.62–50.16), 0.124	1.71 (0.32–9.1), 0.527	
Encephalopathic/brainstem S.			0.60 (0.49–6.6), 0.654	
VA 20/100 at onset[b]				
20/100 (ref)				
≤ 20/100	0.51 (0.17–1.52), 0.227			
[c]DSS at onset				
0–2.5 (ref)				
≥ 3.0			0.61 (0.03–10.7), 0.737	
Maintenance therapy	0.73 (0.19–2.75), 0.641		0.75 (0.11–4.89), 0.764	
Annualized relapse rate	0.57 (0.26–1.26), 0.169	0.56 (0.24–1.29), 0.173	0.64 (0.17–2.49), 0.522	
Categorized MOG-Ab titres				
≤1280 (ref)	–		–	
2560–5120	0.40 (0.07–2.44), 0.320		0.25 (0.03–1.86), 0.176	0.28 (0.02–2.10), 0.183
≥10,240	0.53 (0.09–3.20), 0.490		0.21 (0.02–1.88), 0.164	0.41 (0.03–482), 0.480
Follow-up (months)	1.01 (0.98–1.03), 0.589		0.99 (0.96–1.02), 0.421	

The values are given in bold when there is a significant difference ($p < 0.05$) or when there is a trend differences between groups ($p < 0.080$)

In univariate and multivariate analyses, data were given in OR (95% CI), p value

ON optic neuritis, *Encephalophatic/brainstem S* Encephalic or brainstem syndrome, *DSS* Disability Status Scale, *VA* visual acuity, *MOG-Ab* myelin oligodendrocyte glycoprotein

[a]Among patients starting with a non-ON phenotype, none of the non-Caucasian patients had good motor outcome and, therefore, no comparison was possible in this subgroup

[b]VA at onset is only included in the model among patients starting with a ON phenotype

[c]DSS at onset is only included in the model among patients starting with a non-ON phenotype

higher titres predict a relapsing non-MS course [5]. In the present cohort of MOG-Ab-positive adults, we could not find any association between MOG-Ab titres at the first episode and the risk of relapse. Similarly, the usefulness of titres at the first episode to predict visual or motor outcome was limited. We observed that time to the first relapse was influenced by age and younger patients had a higher risk for relapsing, supporting a likely more active underlying immune activity in this subgroup, in line with a previous study [3]. This age-dependent risk of relapse has also been described in other demyelinating diseases such as MS [25], but not in AQP4-Ab-associated disease [26]. Nonetheless, we found that despite the higher risk of relapse, younger patients had a better prognosis when evaluating motor disability which underlines their greater recovery capability.

Several diagnostic methods have been used to detect MOG-Ab, mainly CBA with immunocytochemistry or flow cytometry as detection procedures [27]. Antibody titration requires multiple steps to dilute the sample, which increases the likelihood of technical error, thus decreasing the chances of maintaining test reproducibility and validity. The positive correlation between MOG-Ab titres and MOG-ratio ΔMFI in different clinical phenotypes indicates that MOG-ratio ΔMFI could be a simple and straightforward method to measure serum MOG-Ab levels, thus helping us to overcome previous mentioned disadvantages. The use of MOG-ratio ΔMFI could also be of interest to select sample patients when performing experimental research. Indeed, antibody concentration seems to play a role in MOG pathophysiology making MOG-ratio ΔMFI useful for selecting those samples with higher MOG-Ab levels [28]. Similar approaches based on ΔMFI have also been used to select specific samples to perform in vitro pathophysiological experiments in AQP4-Ab-associated disease [29].

Currently, we refer to MOG-Ab-associated disease when patients have an ADS with positive MOG-Ab in serum (biological serostatus), regardless of the clinical phenotype at onset or thorough the disease course. In the present study,

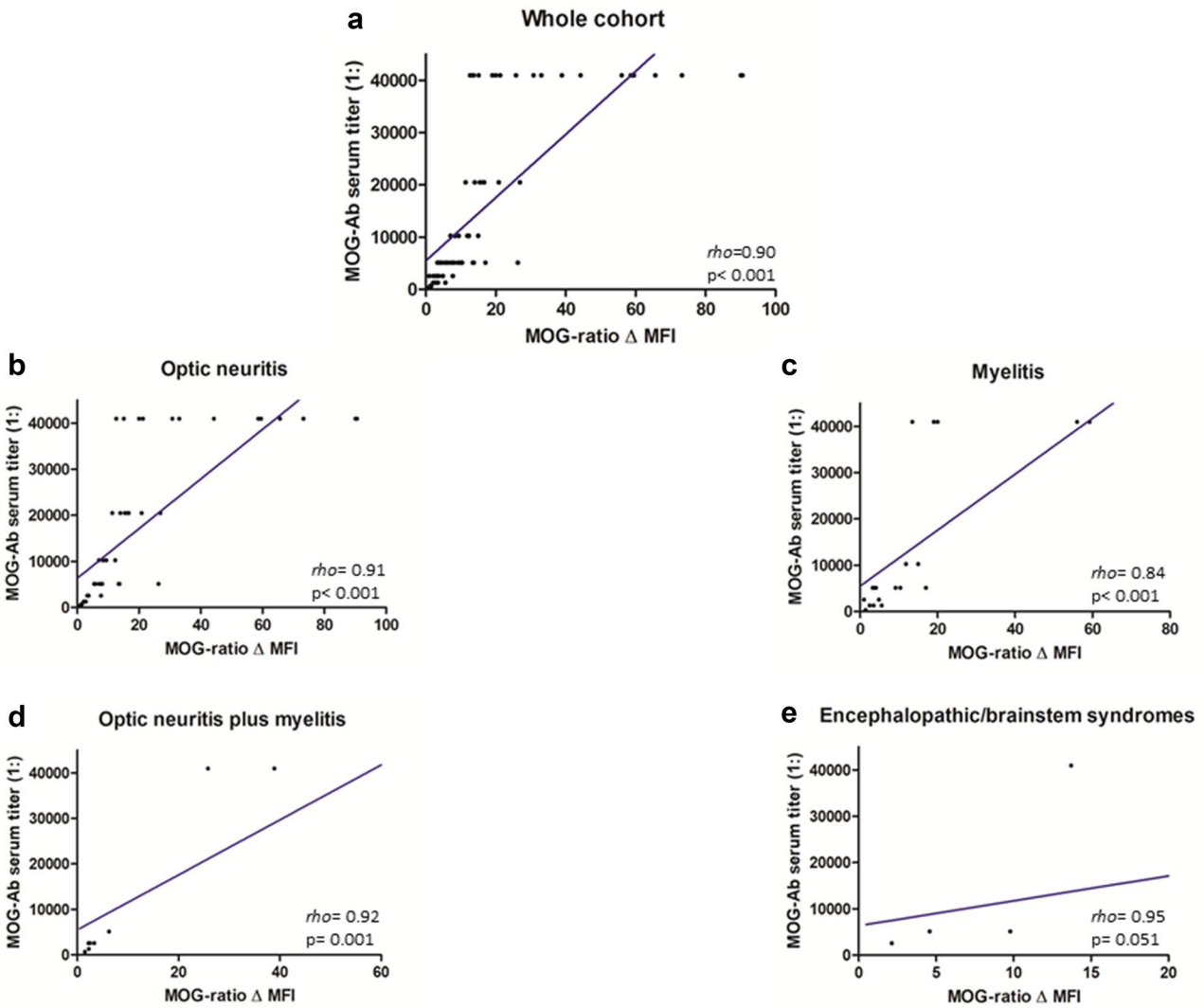

Fig. 2 Correlations between MOG-Ab titres and MOG-ratio ΔMFI. **a** Whole cohort, and regarding clinical phenotype at onset: **b** optic neuritis, **c** myelitis, **d** optic neuritis plus myelitis, **e** encephalopathic/brainstem syndromes

we evaluated the predictive value of MOG-Ab titres in the whole sample without classifying patients according to the clinical phenotypes. This is a rare disease and collaborative studies using same antibody testing are essential to evaluate whether the predictive value of MOG-Ab titres at the first episode could differ among clinical phenotypes.

This study has some limitations that must be addressed. First, we cannot rule out an effect of acute treatment on MOG-Ab titres. However, the association between titres and disability at onset indicates a likely marginal effect of acute treatment. Similarly, although maintenance therapy was not related to outcome in the predictive analysis, dedicated studies evaluating the impact of long-term therapies in MOG-Ab-associated disease deserve to be performed to elucidate the impact of such therapies on outcome and titres. Second, we have to account for a possible selection bias since only patients whose samples were obtained within the first 3 months were included. Patients with atypical phenotypic presentations other than ON or TM at the first episode may have been missed. Recent guidelines on diagnosis of MOG-Ab-associated disease specify the criteria to select patients for MOG-Ab testing [30]. Finally, MOG-Ab-associated disease is usually described as having a benign course, and only a small proportion of patients remain severely disabled at last follow-up. Thus, larger sample size considering time when performing outcome analysis should be performed to confirm our results.

Overall, our findings showed that serum MOG-Ab titres might reflect a more active disease at the earliest time point, but do predict neither further relapse nor disability.

Therefore, MOG-Ab titres at first episode do not seem to be a useful tool to predict disease course. MOG-ratio ΔMFI could be used to determine serum MOG-Ab levels, being an easy and reliable method for diagnostic and research purposes in substitution of MOG-Ab titres.

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Compliance with ethical standards

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