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Short report

# MOG antibody non-P42 epitope is associated with a higher risk of relapse in paediatric MOGAD

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## ABSTRACT

**Background** Biomarkers for predicting myelin oligodendrocyte glycoprotein antibody (Ab)-associated disease (MOGAD) clinical course are still missing. Binding capacity to a mutant MOG protein variant (MOG-P42S; non-P42) was shown to correlate with an increased relapse risk in adult patients.

The objective of our study was to assess the frequency of binding to the non-P42 MOG variant in a cohort of paediatric MOGAD and to investigate its association with specific clinical profiles and disease course.

**Methods** We included children with MOG-Ab seropositive samples collected after their first demyelinating episode from five different centres. We performed live cell-based assays with native full-length MOG (MOG-FL) and mutant MOG-P42S and correlated the results with clinical data.

**Results** Of the 81 MOG-FL identified patients serum, 40 bound the non-P42 MOG. Non-P42 patients exhibited an earlier median age of onset ( $p=0.002$ ). Phenotype distribution was different between groups ( $p=0.001$ ), with non-P42 patients predominantly exhibiting acute disseminated encephalomyelitis phenotype. Notably, the non-P42 group was associated with a higher relapse rate (relative rate: 2.6 (95% CI 1.1 to 6.2),  $p=0.03$ ), adjusted for clinical phenotype.

**Conclusion** Non-P42 is a promising biomarker for predicting relapse in paediatric MOGAD patients.

prognosis and for a better understanding of pathophysiology. Several studies have evaluated the importance of different epitopes of MOG in binding sensitivity and affinity to MOG-Ab.<sup>8–10</sup> An epitope around proline at position 42 in the CC' loop (P42) is important for MOG-Ab binding, where a mutation leading to a replacement of proline with serine (non-P42) results in no binding of MOG-Ab to this native mutant in about 60% of patients.<sup>8</sup> Reduced immunoreactivity to P42 and higher reactivity to non-P42 was associated with relapsing ON.<sup>9</sup> Recently, non-P42 MOG-Ab was shown to predict a relapsing course in a significant subgroup of adult MOGAD patients.<sup>11</sup>

The objective of our study was to evaluate if the epitope binding region around P42 is similarly crucial for binding of MOG-Ab in children and to explore potential associations between non-P42 binding and specific demographic or clinical characteristics in a MOGAD paediatric cohort.

## MATERIALS AND METHODS

### Cohort

This cohort included samples from 81 unselected paediatric MOGAD patients collected in 5 centres: 42 patients from the French nationwide NOMADMUS cohort (Lyon, France), 9 patients from Bicêtre Hospital (Paris, France), 4 patients from St. Josef Hospital (Bochum, Germany), 3 patients from Charité Medical University (Berlin, Germany) and 23 patients from Children's Hospital at Westmead (Sydney, Australia).

Patients who were tested clear seropositive for MOG-Ab using the full-length form, had at least one demyelinating episode of the central nervous system (CNS) persisting for  $\geq 24$  hours and fulfilled the proposed MOGAD criteria<sup>1</sup> were included. The P42 group included sera that only bind to the native MOG full-length (MOG-FL) form, and the non-P42 group included sera that bind to both native FL and native mutant MOG-P42S forms. Demographic (gender, age at disease onset) and clinical data (date of relapses, clinical phenotype at onset, disability measured by Expanded Disability Status Scale and visual acuity) were collected. Data on maintenance therapy (name, starting date and end date) were collected, when available.

## INTRODUCTION

Myelin oligodendrocyte glycoprotein antibody (MOG-Ab) associated disease (MOGAD) is a rare neuroinflammatory disorder associated with several clinical phenotypes.<sup>1–3</sup> The most common clinical phenotype in prepubertal children is acute encephalomyelitis (ADEM), whereas optic neuritis (ON) is the most frequent in adults.<sup>4</sup> The clinical course is unpredictable and ranges from monophasic to highly relapsing. At 2 years of follow-up, as many as 50% of patients may experience a relapse.<sup>1–3</sup> No clear prognostic biomarkers of outcome have been identified yet. Persistent seropositive status has been associated with a higher risk of relapse, as well as serum antibody titre at onset or follow-up, or MOG-Ab positivity in the cerebrospinal fluid, but the latter is still controversial.<sup>4–7</sup> Qualitative evaluation of MOG-Ab is also of interest both for



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### Live cell-based assay for immunoreactivity to MOG-FL (P42) and MOG-P42S (non-P42)

Live cell-based assays were performed in the Lyon Neuroscience Research Center.<sup>12</sup> HEK293 cells were transfected with either the full-length pEGFPN1-hMOG plasmid (MOG-LF, P42) or the mutant pEGFPN1-hMOG-P42S (non-P42). Serum samples were used at a dilution of 1:640. Allophycocyanin (APC)-Goat anti-human IgG-Fcγ fragment-specific (Jackson ImmunoResearch, 109-136-170) was used as a secondary antibody. ACS analysis for MOG-FL (P42) and MOG-P42S (non-P42) was performed with the CANTO II flow cytometer (Becton Dickinson).

### Statistical analysis

Continuous variables were described by median and IQR, and categorical variables by count and percentage. The association between P42/non-P42 status and demographical and clinical variables was evaluated using non-parametric univariate tests: Fisher's exact test for categorical variables and Wilcoxon sum rank test for continuous variables. The relapse rate was analysed for all patients with an available longitudinal follow-up using a negative binomial model to account for overdispersion, with the logarithm of follow-up duration as offset, and P42/non-P42 status and disease phenotype as fixed effects. P values below 0.05 were considered statistically significant. Analyses were performed using R software, V.4.0.3 (R Core Team (2023). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org>).

## RESULTS

### Demographic and clinical data of the whole cohort

The paediatric MOGAD cohort consisted of 81 patients aged less than 18 years at the time of disease onset. There was a female/male ratio of 0.93. The median age at onset was 8.0 years (IQR: 4.7–12.0 years). Samples were collected during relapse in 27 (33.3%) patients, in a remission phase in 37 (45.7%) patients, and information was not available for 17 (21.9%) patients. The clinical phenotype at presentation was ADEM for 38 patients (46.9%), ON for 23 (28.4%), myelitis for 10 (12.3%), combination of ON and myelitis for 8 (9.9%) and 2 (2.5%) had brainstem involvement.

### Demographic and clinical data according to binding capacity to non-P42 variant

Overall, 40 (49.4%) MOG-Ab from patient sera demonstrated binding to both P42 and non-P42. Patients in the non-P42 group were younger than those in the P42 group, with a median age at disease onset of 6.2 years (IQR: 4–9.2 years), vs 10.0 years (IQR: 6.4–14 years;  $p=0.002$ ). There was no difference in gender distribution between the two groups. The non-P42 and P42 groups had a distinct phenotype distribution ( $p=0.001$ ): 28 (73.7%) out of 38 ADEM patients belonged to the non-P42 group, whereas only 7 (30.4%) out of 23 ON patients were non-P42, 3 (30.0%) out of 10 TM patients, and 2 (25.0%) out of 8 patients with both ON and TM [table 1](#).

### Sample characteristics according to binding capacity to non-P42 MOG

Samples from patients in the non-P42 group were collected earlier in the course of disease (median of 0.1 years (IQR: 0.0–0.9 years)) compared with the P42 group (median of 0.7 years (IQR: 0.1–4.1 years);  $p=0.007$ ). Additionally, 17 (63.0%) patients in the non-P42 group were in relapse at the time of sample collection, compared with only 10 (27.0%) patients in the P42 group ( $p=0.005$ ). In four patients (two from P42 and two from non-P42 groups), serial sampling was performed and revealed stability of non-P42 binding.

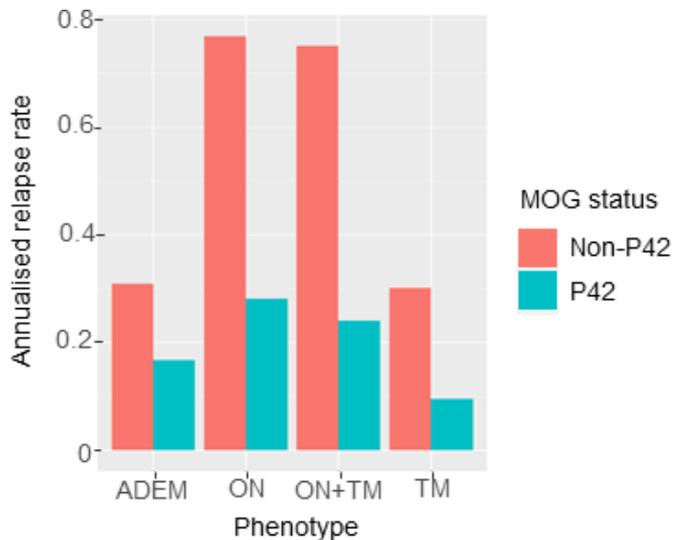
### Clinical course

Among the 59 patients with a longitudinal follow-up, 35 out of 59 (60%) were relapsing, and 111 relapses were reported over 389 person-years of follow-up, with annualised relapse rates (ARRs) of 0.29. When comparing the two groups, patients in the non-P42 group presented higher relapse rates (relative rate: 2.6 (95% CI: 1.1 to 6.2),  $p=0.03$ ), adjusted for clinical phenotype. The difference between the P42 and non-P42 groups was observed among all clinical phenotypes. ARR in ADEM patients was 0.31 in the non-P42 group vs 0.17 in the P42 group, in ON patients it was 0.77 in the non-P4 group vs 0.28 in the P42 group, in TM patients 0.30 in the non-P42 group vs 0.10 in the P42 group, and in patients with both ON and TM the ARR was 0.75 in the non-P42 group vs 0.24 in the P42 group ([figure 1](#)).

**Table 1** Comparison between MOG P42 and non-P42 paediatric populations

		P42 n=41	Non-P42 n=40	P value
Gender	Female n (%)	20 (48.8)	19 (47.5)	1.000
Age at onset	Median (IQR)	10.0 (6.4–14.1)	6.2 (4.0–9.2)	0.002
Phenotype at onset	ADEM n (%)	10 (24.4)	28 (70.0)	0.001
	ON n (%)	16 (39.0)	7 (17.5)	
	ON+TM n (%)	6 (14.6)	2 (5.0)	
	TM n (%)	7 (17.1)	3 (7.5)	
	Other n (%)	2 (4.9)		
EDSS at onset	Median (IQR)	3.0 (0.0–6.5)	2.2 (0.0–3.1)	0.247
Sampling at onset	n (%)	18 (47.4)	18 (45.0)	1.000
Interval between onset and sample collection	Median (IQR)	0.7 (0.1–4.1)	0.1 (0.0–0.9)	0.007
EDSS at sample collection time	Median (IQR)	1.2 (0.0 to 4.0)	2.0 (0.0 to 2.9)	0.674
Sampling during attack	yes n (%)	10 (27.0)	17 (63.0)	0.005
Sampling under treatment	yes n (%)	17 (54.8)	15 (62.5)	0.595
Duration of follow-up	Median (IQR)	1162.8 (303.8–2839.6)	899.0 (255.3–3109.0)	0.618

ADEM, acute disseminated encephalomyelitis; EDSS, Expanded Disability Status Scale; ON, optic neuritis; TM, transverse myelitis.



**Figure 1** Annualised relapse rate in non-P42 versus P42 groups in each clinical phenotype. ADEM, acute disseminated encephalomyelitis; ON, optic neuritis; TM, transverse myelitis.

## DISCUSSION

Our study is the first to investigate the prevalence and prognostic value of the MOG antibody non-P42 epitope in a large paediatric MOGAD cohort. We found that half of paediatric patients with MOG-Ab seropositivity recognised non-P42 MOG, and that the paediatric non-P42 patients were younger at disease onset, were more likely to present with an ADEM phenotype, and had a higher risk of relapse.

The over-representation of ADEM phenotype in the non-P42 group may be attributed to the ability of MOG-Ab in ADEM to recognise and bind more diverse epitopes of MOG, thereby allowing for a broader range of antigenic targets. Indeed, ADEM is classically characterised by multifocal demyelinating lesions in various regions of the CNS. In addition, ADEM has been associated with previous vaccination or infection, and it is possible that an immune trigger leads to global CNS inflammation, resulting in a broader MOG-Ab repertoire that can recognise multiple MOG epitopes.<sup>8</sup>

We found an association between non-P42 and future relapse risk. This is in line with the recent study from Liyanage *et al* showing that non-P42 MOG-Ab epitope is predictive of relapse in adult patients with unilateral ON.<sup>11</sup> Despite a different phenotype at clinical presentation,<sup>4</sup> we confirm in a paediatric population that the non-P42 epitope could be useful as well in paediatric patients to predict a future risk of relapse and could impact the therapeutic strategy regarding chronic maintenance therapy, especially in the setting of a first episode of ADEM. In children, evolution may be monophasic with a good motor outcome. Nevertheless, cognition can be frequently impaired, and residual epilepsy is possible. Clinical outcomes of relapse after ADEM are associated with various sequelae including motor or cognitive deficits, seizures or residual visual impairment.<sup>13–15</sup>

There are some limitations to our study. First, it has been performed in a limited number of patients. However, the inclusion of five different clinical centres prevents the risk of selecting specific populations and increases the generalisability of these results. In the same line, as our study included only expert centres, one cannot exclude an over-representation of relapsing MOGAD. A prospective study on unselected consecutive cases is needed to further validate our findings. Second, the non-P42

group of patients was sampled earlier in the course of disease and were more frequently evaluated during an active phase. However, in the previous work from the Australasian MOGAD study group, MOG-Ab epitope status remained highly stable over time, and thus did not appear to be influenced by the period of sampling nor the disease duration.<sup>9 11</sup>

Our work suggests that MOG non-P42 is an important biomarker for predicting relapse in paediatric MOGAD patients, with the added advantage of being easy to evaluate.

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**Contributors** RM, AG and AEH had full access to all of the data in the study and RM is responsible for the overall content as guarantor. RM and AEH contributed to the conception, design of the study. AG contributed to statistical analyses. All authors contributed to acquisition, analysis and interpretation of data. AEH, AG and RM contributed to drafting the text and preparing the figures. All authors contributed to the critical review of the manuscript for important intellectual content. RM obtained funding and supervised AEH.

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and the Sumaira Foundation. FB has received research funding from the MOG Project, NSW Health, MS Australia, the National Health Medical Research Council (Australia), the Medical Research Future Fund (Australia) and investigator-initiated research grant from Novartis. She was on an advisory boards for Novartis, Merck and The MOG Project and the Sumaira Foundation and has been an invited speaker for Biogen, Novartis and Limbic Neurology Her lab offers MOG-IgG testing (at no cost to patient and families). RM serves as a consultant on an advisory board for Alexion and UCB and has been an invited speaker for educational/research sessions coordinated by Biogen, Alexion, UCB, Novartis and Roche. He is on the medical advisory board (non-remunerated positions) of The MOG Project and the Sumaira Foundation.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by the French data protection agency (Commission Nationale de l'Informatique et des Libertés (CNIL); authorisation request 914066v3) and a French ethical committee (Comité de Protection des Personnes (CPP): reference 2019-A03066-51). Computer processing of the data in this study is registered with the Commission Nationale de l'Informatique et des Libertés register of the Hospices Civils de Lyon (reference methodology MR004, no. 21\_5840). Participants gave informed consent to participate in the study before taking part.

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