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► **To cite this version:**

Alvaro Cobo-Calvo, Anne Ruiz, Elisabeth Maillart, Bertrand Audoin, H el ene Z ephir, et al.. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: The MOGADOR study. *Neurology*, 2018, 90 (21), pp.e1858-e1869. 10.1212/WNL.0000000000005560 . hal-01919569

HAL Id: hal-01919569

<https://hal.science/hal-01919569v1>

Submitted on 3 Dec 2024

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Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults

The MOGADOR study

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Neurology® 2018;0:e1-e12. doi:10.1212/WNL.0000000000005560

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Abstract

Objective

To describe clinical and radiologic features associated with myelin oligodendrocyte glycoprotein antibodies (MOG-Ab) in a large French nationwide adult cohort, to assess baseline prognostic features of MOG-Ab-associated diseases after a first acute demyelinating syndrome, and to evaluate the clinical value of MOG-Ab longitudinal analysis.

Methods

Clinical data were obtained from 197 MOG-Ab-positive patients ≥ 18 years of age. Complete imaging data were available in 108, and 54 serum samples were eligible for longitudinal evaluation. For survival analysis comparison, 169 aquaporin-4 antibody (AQP4-Ab)-positive patients from the NOMADMUS database were included.

Results

Median age at onset was 36.46 (range 18.0–76.8) years, and patients were predominantly white (92.9%) with male:female ratio, 1.1. Clinical phenotype at onset included optic neuritis or myelitis in 90.86%, isolated brainstem or encephalopathy syndromes in 6.6%, and a combination of syndromes in 2.5%. Distinctive brain MRI findings in MOG-Ab-positive patients were thalamic and pontine lesions. Cortical and leptomeningeal lesions were found in 16.3% and 6.1%, respectively. The probability of reaching a first relapse after 2 and 5 years was 44.8% and 61.8%, respectively. MOG-Ab-positive patients were at lower risk at presentation of further clinical relapse (hazard ratio [HR] 0.45, 95% confidence interval [CI] 0.26–0.79) compared to AQP4-Ab-positive individuals. MOG-Ab-positive individuals had a lower risk of reaching Disability Status Scale score of 3.0 (HR 0.46, 95% CI 0.22–0.94) and visual acuity of 20/100 (HR 0.23, 95% CI 0.07–0.72). Finally, MOG-Ab titers were higher at relapse than in remission ($p = 0.009$).

Conclusion

In adults, MOG-Ab-associated disease extends beyond clinical and radiologic abnormalities in the optic nerve and spinal cord. Despite the relapsing course, the overall visual and motor outcome is better compared with AQP4-Ab-positive patients.

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Editorial

Time to separate MOG-Ab-associated disease from AQP4-Ab-positive neuromyelitis optica spectrum disorder

Page 947

Glossary

ADS = acquired demyelinating syndromes; AQP4-Ab = aquaporin-4 antibodies; CI = confidence interval; DSS = Disability Status Scale; EDSS = Expanded Disability Status Scale; FLAIR = fluid-attenuated inversion recovery; HR = hazard ratio; IgG = immunoglobulin G; IQR = interquartile range; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; OCB = oligoclonal band; OFSEP = Observatoire Français de la Sclérose en Plaques; ON = optic neuritis; TM = transverse myelitis; VA = visual acuity.

Antibodies directed against myelin oligodendrocyte glycoprotein (MOG-Ab) have been reported in the serum of pediatric patients with non-multiple sclerosis (MS) acquired demyelinating syndromes (ADS) and in adult patients with neuromyelitis optica spectrum disorders (NMOSDs).¹⁻⁴

In adult patients with NMOSD, MOG-Ab seem to define a clinically homogeneous subgroup with distinctive findings compared to aquaporin-4 antibody (AQP4-Ab)-positive patients: younger age at onset, more frequently male, and an optic nerve preference.^{1-3,5,6} Reports of new clinical phenotypes such as cortical encephalitis or brainstem syndromes and cases with fulminating course suggest that the whole clinical and radiologic spectrum is not yet fully defined.⁷⁻¹¹

MOG-Ab-positive patients were initially associated with a monophasic and less severe disease course compared to AQP4-Ab-positive cases.¹⁻³ Recently, a longer follow-up time revealed a higher frequency of relapses than initially described with potentially more important disability.^{9,12} However, these studies were based on small cohorts of patients, mixed features from adults and pediatrics, and did not consider time when performing outcome analysis. Thus, whether MOG-Ab are related to a better prognosis than AQP4-Ab in ADS is currently a matter of debate.

Some studies have reported that a decrease of MOG-Ab titers and seronegative conversion are related to both the absence of relapses and a more benign course of the disease.¹³⁻¹⁶ Others have not found this association.^{3,8}

In the present study, we aimed to describe clinical and radiologic features associated with MOG-Ab in a large French nationwide adult cohort, to assess baseline prognostic features of MOG-Ab-associated diseases after a first ADS, and to evaluate the clinical value of MOG-Ab longitudinal analysis.

Methods

Participants

We retrospectively recruited patients from all the French referral centers for neuroinflammatory disorders within the scope of the Observatoire Français de la Sclérose en Plaques (OFSEP) who fulfilled the following inclusion criteria: diagnosis of an ADS, defined as at least 1 acute clinical demyelinating episode of the CNS persisting for a minimum of 24 hours; presence of MOG-Ab in serum detected either at onset of disease or during follow-up; and age ≥ 18 years at onset of disease.

Procedures

Clinical

All requested information was collected in a standardized evaluation form dedicated to the MOGADOR study on the MOG-Ab spectrum in France between January 2014 and January 2017 and registered in the French nationwide database for NMOSDs and associated neurologic disorders (NOMADMUS). The MOGADOR standardized evaluation form includes (1) epidemiologic data such as sex, age at disease onset, and white ethnicity; (2) clinical data such as disability at nadir of symptoms evaluated with the Expanded Disability Status Scale (EDSS), clinical phenotype at onset, number of relapses, clinical phenotype at relapse and at last follow-up, time to first relapse, time to irreversible motor disability (Disability Status Scale [DSS] score of 3.0 and 6.0 persisting for >6 months), and time to irreversible visual disability (defined as visual acuity [VA] of 20/100 persisting for >6 months in at least 1 eye with the Visual Functional System)⁶; (3) biological data such as CSF cell count (pleocytosis >5 cells/mm³) and oligoclonal bands (OCBs) or immunoglobulin G (IgG) index; and (4) short-term and maintenance therapy (immunosuppressants [rituximab, azathioprine, mycophenolate mofetil, mitoxantrone, cyclophosphamide or methotrexate], MS disease-modifying drugs, or low-dose corticosteroids for at least 6 months).

Additional epidemiologic and clinical features such as concomitant autoimmune diseases, infections before disease onset, and other accompanying symptoms at onset (seizures, neuropathic pain, area postrema syndrome) were assessed when available ($n = 144$).

For prognosis analysis, we used 2 different scales (DSS and VA) to differentiate motor and visual outcomes after the first ADS. For motor disability, we included all patients who presented with non-optic neuritis (ON) phenotypes, and when evaluating visual disability, we included only those who presented with ON at first ADS.

Final diagnosis

Two clinicians (A.C.-C and R.M.) reviewed all cases and neuroimaging and classified patients as having acute disseminated encephalomyelopathy,¹⁷ NMOSD,¹⁸ other limited NMO-like phenotypes (i.e., isolated monophasic or relapsing transverse myelitis [TM] or ON), MS,¹⁹ and brainstem syndromes. Patients with short TM and ON who did not strictly fulfill NMOSD criteria were classified as optico-spinal phenotype.¹⁸

MOG-Ab cohorts

We defined an incident cohort considering only patients whose disease began after January 2014 (availability date of MOG-Ab test in our laboratory) and whose diagnosis was made shortly after the onset of symptoms. The remainder were defined as the retrospective cohort. Both cohorts (incident and retrospective) belonged to the whole cohort of the present study that was used for clinical and prognosis analysis.

AQP4-Ab cohort

Epidemiologic and clinical data from AQP4-Ab-positive patients were extracted from the files included in the NOMADMUS database during the study period²⁰ (appendix e-1, links.lww.com/WNL/A474).

Radiologic

Available brain and spinal cord MRIs within 3 months from onset of symptoms were evaluated (which did not routinely include orbital MRI). Images were assessed by 2 independent raters blinded to the clinical and antibody results using the Picture Archiving and Communication System. MRI studies included axial and sagittal images of the brain and spinal cord obtained by T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and T1-weighted postcontrast sequences. When an abnormal brain MRI was registered, features known to be associated with NMOSDs²¹ and features recently reported in patients with MOG-Ab²² were noted: (1) predominantly cortical gray matter, (2) hazy/poorly demarcated lesions, (3) confined to basal ganglia and/or brainstem tumefactive lesions, (4) nonspecific white matter lesions, or (5) gadolinium enhancement. Topography of the lesion was also collected (appendix e-2, links.lww.com/WNL/A474).

As controls, we used the most recent available abnormal brain MRI from our cohort of AQP4-Ab-positive patients.

Autoantibody detection

Within the period of the study, 16,181 serum samples were tested for AQP4-Ab and MOG-Ab by cell-based assay with live HEK293, as previously described.^{20,23} Titration of MOG-Ab-positive samples was performed in a second step with serum samples stored at the Neurobiotec biobank (Lyon University Hospital, France) by serial dilution until loss of positive signal (from 1:160 to 1:40,000). We used a secondary anti-Fc to avoid immunoglobulin M cross-reactivity.²⁴ We performed a longitudinal analysis of MOG-Ab titers in patients with available samples obtained at least 3 months apart. Relapsing samples were defined as those collected within 3 months from episode; remission samples were collected at least 3 months from the episode.¹⁶

Statistical analysis

For prognostic analysis, we consider the whole MOGADOR cohort, and we performed a univariate analysis with the estimation of the cumulative event rates between the MOG and AQP4-Ab groups using Kaplan-Meier method expressing 95%

confidence intervals (CIs). Survival curve comparison was carried out by the log-rank test. A univariate Cox proportional hazard model was used to compare time to event between both groups, and baseline variables with a value of $p \leq 0.10$ were included in the multivariate model. Maintenance therapy was included as a time-varying covariate in both analyses.

The clinical and demographics characteristics between MOG-Ab patients and AQP4-Ab patients were compared by use of the χ^2 test (or Fisher exact test) for categorical variables and the t test (or nonparametric Wilcoxon-Mann-Whitney test) for continuous variables.

For serum longitudinal analysis, the Wilcoxon-Mann-Whitney test was used to compare relapsing and remission samples, and the Wilcoxon matched-pairs rank-sum test was used for samples during follow-up.

All statistical analyses were performed with STATA-12 software (64-bit, StataCorp, College Station, TX) and GraphPad Prism (version 5.0, GraphPad Software, La Jolla, CA). Values of $p < 0.05$ were considered significant.

Standard protocol approvals, registrations, and patient consents

The study was conducted in accordance with the French law relative to clinical noninterventional research. According to the French law on bioethics (July 29, 1994; August 6, 2004; and July 7, 2011, Public Health Code), the patients' written informed consent was collected. Moreover, data confidentiality was ensured in accordance with the recommendations of the French commission for data protection (Commission Nationale Informatique et Liberté, CNIL decision DR-2014-558).

Data availability

This study was done within the framework of OFSEP. Because of national confidentiality requirements, only anonymized data, not pseudonymized data, can be shared. 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) and with respect to French law.

Results

Clinical description of MOG-Ab-positive patients

Epidemiology, clinical presentation, and treatment choice

We identified 197 MOG-Ab-positive patients in the whole cohort, and none of them were AQP4-Ab-positive. Among them, 50.8% were male (male:female ratio 1.1), and the median age at presentation was 36.5 (interquartile range [IQR], 28.2–47.7) years. Patients were predominantly white (92.9%).

A background of autoimmune disease was observed in 16 of 144 (11%) patients, and 20% of patients had a history of infection within 1 month after disease onset (table 1).

The most frequent clinical phenotypes at onset were ON (60.9%) and then myelitis (22.3%), and 7.6% of patients developed simultaneous ON and myelitis. ON was bilateral in 50 of 120 (41.7%) patients presenting with ON at onset. Among the 15 patients with ON and myelitis as the initial picture, 6 (40%) had bilateral ON. At presentation, 18 (9.1%) patients had an initial presentation other than ON and/or myelitis, 8 (4.1%) developed an isolated brainstem syndrome, 5 (2.5%) had an isolated encephalopathic syndrome, 4 (2.0%) had a brainstem syndrome together with encephalopathy, and 1 (0.5%) had ON together with brainstem syndrome. Other less frequent accompanying symptoms at onset were neuropathic pain (7.6%), fever (9%), and area postrema symptoms (2.1%), and 2 (1.4%) patients developed seizures (table 1).

After a review of 144 clinical reports, previous or concomitant autoimmune diseases were found in 16 (11.1%) patients: hypothyroidism in 6 (37.5%), psoriasis in 4 (25%), sarcoidosis in 2 (12.5%), and Sjögren syndrome, Guillain-Barre syndrome, autoimmune hepatitis, and myasthenia gravis in 1 (6.3%) patient each. Moreover, autoantibodies were found in 29 (20.1%) patients (table 1). Baseline features regarding phenotype at onset are depicted in table e-1 (links.lww.com/WNL/A473).

Only 10 of 175 (5.7%) and 7 of 96 (7.3%) patients had OCB or positive IgG index in the CSF, respectively. Pleocytosis in CSF was observed in 61 of 138 (44.2%) patients and was seen most frequently in those presenting with myelitis at onset (30 of 38, 79.0%) compared to the remainder (31 of 100, 31%, $p < 0.001$) (table e-1, links.lww.com/WNL/A473).

Most patients (83.8%) received acute-phase treatment at onset. Maintenance therapy was started in 34 of 197 (17.3%) patients in the 3 months after presentation and in 40 of 83 (48.2%) patients in the 3 months after the first relapse. Overall, at the final follow-up, maintenance therapy had been started in 115 of 197 (58.4%) patients and in 67 of 83 (80.7%) of those who relapsed. Immunosuppressants were administered in 106 (53.8%) patients at least once during the course of the disease; 45 (43.3%) received rituximab, 36 (34.6%) received azathioprine, and 38 (33.7%) received mycophenolate mofetil. When all patients treated with maintenance therapy are taken into account, rituximab was the first-choice treatment in 33 of 115 (28.7%), followed by azathioprine in 31 of 115 (27%) and mycophenolate mofetil in 28 of 115 (24.4%). Other treatments less frequently used were mitoxantrone, cyclophosphamide, or methotrexate in 12 of 197 (6.1%) patients; MS disease-modifying drugs in 8 of 197 (4.1%); and corticosteroids in 11 of 197 (5.6%).

Patients with myelitis at onset were more frequently treated (29 of 59, 49.2%) compared to patients starting with ON (24 of 120, 20%) or other clinical phenotypes (4 of 18, 22.2%, $p < 0.001$).

Disease course, outcome, and clinical phenotype at last follow-up

In the whole cohort, 83 of 197 (42.1%) patients relapsed after a median follow-up of 15.8 (IQR 7.2–50.1) months. In the whole cohort, the cumulative risk to reach a relapse after 2 and 5 years was 44.8% and 61.8%, respectively (figure e-1A, links.lww.com/WNL/A472). At 2 years, 43.1% (95% CI 31.6%–56.8%) in the 139-patient incident cohort and 43.8% (95% CI 30.0%–60.6%) in the 58-patient retrospective cohort experienced a relapse (log-rank $p = 0.617$) (figure e-1B). The whole cohort was globally characterized by a favorable motor and visual prognosis at the last follow-up. However, we found that 19 of 77 (24.7%) patients presenting with non-ON phenotypes reached a DSS score of 3.0 and 8 of 77 (10.4%) reached a DSS score of 6.0. Regarding visual disability, 11 of 136 (8.1%) patients who presented with ON reached VA of 20/100 at the last follow-up (table 1). There were no differences in the proportion of patients who reached a DSS score of 3.0 or VA of 20/100 between relapsing and monophasic patients (data not shown).

At the last follow-up, 38 (19.3%) patients fulfilled criteria for NMOSDs, and 3 (1.5%) patients fulfilled criteria for MS. Clinical phenotypes at the last follow-up are shown in table 1 and figure e-2 (links.lww.com/WNL/A472).

Radiologic features in MOG-Ab-associated diseases

We were able to evaluate 108 brain MRIs, and 49 (44.4%) of them were found to be abnormal. Among patients with ON or myelitis at onset, 23 of 72 (31.9%) and 16 of 30 (53.3%), respectively, displayed abnormalities on the first available brain MRI (table e-2, links.lww.com/WNL/A473).

Patients presenting with an abnormal brain MRI had higher disability at onset than those with normal brain MRI ($p = 0.006$). Moreover, 64.9% of patients with abnormal brain MRI displayed CSF pleocytosis compared to 27.3% without brain MRI abnormalities ($p = 0.001$). OCBs in CSF were found exclusively in patients with brain MRI abnormalities ($p = 0.064$). Finally, autoantibodies were seen more frequently in patients with abnormal brain MRI ($p = 0.035$) (table e-2, links.lww.com/WNL/A473).

We did not identify a specific radiologic pattern in the MOG-Ab group compared to the AQP4-Ab group ($n = 22$). However, lesions located in the thalamus and pons were more frequently seen in the MOG-Ab group ($p = 0.031$ and $p = 0.007$, respectively), while lesions in medulla oblongata and area postrema were more frequently observed in the AQP4-group ($p = 0.004$ and $p < 0.001$, respectively) (table 2). Other findings were cortical involvement in 8 (16.3%) and leptomeningeal enhancement in 3 (6.1%) patients. Representative cases of pathologic brain MRI are shown in figure 1. A description of patient characteristics with cortical involvement appears in table e-3, links.lww.com/WNL/A473, and figure e-3, links.lww.com/WNL/A472.

Table 1 Epidemiologic and clinical characteristics in MOG-Ab-positive patients

Variables from MOGADOR standardized evaluation form	Whole cohort (n = 197)	Incident cohort (n = 139)	Retrospective cohort (n = 58)
Female, n (%)	97 (49.24)	66 (47.48)	31 (53.45)
Age at onset, median (range), y	36.46 (18.97–76.75)	37.37 (18.97–76.75)	34.26 (19.22–65.03)
White, n (%)	183 (92.89)	127 (91.37)	56 (96.55)
FU, median (range), mo	15.77 (1–556.64)	10.78 (1–37.55)	90.51 (18.6–556.64)
Phenotype at onset, n (%)			
All ON	120 (60.91)	89 (64.03)	31 (53.45)
Unilateral ON	70 (35.53)	52 (37.41)	18 (31.03)
Bilateral ON	50 (25.38)	37 (26.62)	13 (22.41)
Myelitis	44 (22.34)	25 (17.99)	19 (32.76)
ON and myelitis	15 (7.61)	12 (8.63)	3 (5.17)
Brainstem syndrome	8 (4.06)	4 (2.88)	4 (6.90)
Encephalopathic syndrome	5 (2.54)	5 (3.60)	0
Brainstem and encephalopathic syndrome	4 (2.03)	3 (2.16)	1 (1.72)
Brainstem syndrome and ON	1 (0.51)	1 (0.72)	0
EDSS score at onset, median (range)	3 (0–9.5)	3 (0–9.5)	3 (0–8)
Relapsing disease, n (%)	83 (42.13)	37 (26.62)	46 (79.31)
ARR, mean (SD)	0.37 (0.79)	0.38 (0.92)	0.31 (0.29)
Acute-phase treatment (MTP/Ig/PLEX), n (%)	165 (83.76)	123 (88.49)	42 (72.41)
Maintenance therapy at last FU, n (%)	115 (58.38)	69 (49.64)	46 (79.31)
Laboratory data^a			
CSF OCB, n (%)	10/175 (5.71)	4/124 (3.23)	6/51 (11.76)
CSF pleocytosis (>5 cells/mm ³)	61/138 (44.20)	48/112 (42.86)	13/26 (50)
CSF IgG index, n (%)	7/96 (7.29)	2/68 (2.94)	5/28 (17.86)
Autoantibodies, n (%) ^b	29/144 (20.13)	22/110 (20)	7/34 (20.59)
Disease onset–MOG sampling time, median (IQR), mo	1.33 (0.36–26.73)	0.56 (0.26–2.07)	67.88 (38.34–123)
Clinical phenotype at last FU, n (%)			
Isolated ON	106 (53.81)	84 (60.43)	22 (37.93)
Monophasic ON	72 (36.55)	65 (46.76)	7 (12.07)
Recurrent ON	34 (17.26)	19 (13.67)	15 (25.86)
NMOSDs	38 (19.29)	18 (12.95)	20 (34.48)
Isolated LETM	24 (12.18)	17 (12.23)	7 (12.07)
Monophasic LETM	20 (10.15)	17 (12.23)	3 (5.17)
Recurrent LETM	4 (2.03)	0	4 (6.90)
ADEM	9 (4.57)	9 (6.47)	0
MS	3 (1.52)	2 (1.44)	1 (1.72)
Isolated non-LETM	8 (4.06)	4 (2.88)	4 (6.89)
Monophasic non-LETM	5 (2.54)	4 (2.88)	1 (1.72)
Recurrent non-LETM	3 (1.52)	0	3 (5.17)

Continued

Table 1 Epidemiologic and clinical characteristics in MOG-Ab-positive patients (continued)

Variables from MOGADOR standardized evaluation form	Whole cohort (n = 197)	Incident cohort (n = 139)	Retrospective cohort (n = 58)
Monophasic brainstem syndrome	5 (2.54)	4 (2.88)	1 (1.72)
Optico-spinal phenotype	4 (2.03)	1 (0.72)	3 (5.17)
Disability at last FU, n (%)			
DSS score $\geq 3.0^c$	19/77 (24.68)	11/50 (22)	8/27 (29.63)
DSS score $\geq 6.0^c$	8/77 (10.39)	6/50 (12)	2/27 (7.41)
VA of 20/100 ^d	11/136 (8.09)	6/102 (5.88)	5/34 (14.71)
Patients who died, n (%)	1 (0.51)	1 (0.72)	0
Additional features from reviewed clinical reports			
Autoimmune disease, n (%) ^e	16/144 (11.11)	12/110 (10.91)	4/34 (11.76)
Previous infection, n (%)	29/144 (20.14)	22/111 (19.82)	7/33 (21.21)
Other symptoms at onset, n (%)			
Area postrema symptoms	3/144 (2.08)	3 (2.75)	0
Fever	13/144 (9.02)	10/111 (9.01)	3/33 (9.09)
Seizures	2/144 (1.39)	1/109 (0.92)	1/35 (2.86)
Neuropathic pain	11/144 (7.64)	8/109 (7.34)	3/35 (8.57)

Abbreviations: ADEM = acute disseminated encephalomyelopathy; ANA = antinuclear antibody; ARR = annualized relapse rate; ANCA = antineutrophil cytoplasmic antibodies; DSS = Disease Status Scale; EDSS = Expanded Disability Status Scale; FU = follow-up; Ig = immunoglobulin; IgG = immunoglobulin G; IQR = interquartile range; LETM = longitudinal extensive transverse myelitis; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; MS = multiple sclerosis; MTP = methylprednisolone; NMOSD = neuromyelitis optica spectrum disorder; OCB = oligoclonal bands; ON = optic neuritis; PLEX = plasma exchange; VA = visual acuity.

^a Only lumbar punctures performed within 1 month from onset of symptoms were considered.

^b Autoantibodies (percent among 29 patients with positive autoantibodies): ANA 1:160, 15 (51.72%); ANCA 1:160, 4 (13.79%); SSb/SSa, 3 (10.34%); thyroid peroxidase, 3 (10.34%); cryoglobulin, 2 (6.90%); anti-synthetase, 1 (3.35%); smooth muscle antibodies, 1 (3.45%); anti-annexin antibodies, 1 (3.45%); and β -2 glycoprotein-1 antibodies, 1 (3.45%).

^c For motor disability comparison (DSS score ≥ 3 and ≥ 6), patients who presented with non-ON phenotypes at first acute demyelinating syndrome were included.

^d For visual disability (VA of 20/100), only patients who presented with ON at first acute demyelinating syndrome were included.

^e Autoimmune disease (percent among 16 patients with autoimmune diseases): hypothyroidism, 6 (37.5%); psoriasis, 4 (25%); sarcoidosis, 2 (12.5%); Sjögren syndrome, 1 (6.25%); Guillain-Barre syndrome, 1 (6.25%); autoimmune hepatitis, 1 (6.25%); and myasthenia gravis, 1 (6.25%).

We obtained 25 brain MRIs at follow-up in the MOG-Ab group, showing complete resolution of lesions in 13 (52%), improvement in 5 (20%), and stability in 6 (24%) patients. Among MOG-Ab-positive patients presenting with isolated myelitis or myelitis together with ON at onset, 27 of 32 (84.4%) and 5 of 9 (55.56%), respectively, depicted longitudinal extensive TM (lesion expanding ≥ 3 contiguous vertebral segments) ($p = 0.065$) (table e-1, links.lww.com/WNL/A473). Thoracic segment was observed in most of the cases (27 of 41, 65.9%).

Outcome of MOG-Ab compared to AQP4-Ab status

Baseline differences between MOG-Ab- and AQP4-Ab-positive patients are given in table e-4 (links.lww.com/WNL/A473). Time to first relapse was influenced by serostatus, and MOG-Ab-positive patients were at lower risk to reach a first relapse (hazard ratio [HR] 0.45, 95% CI 0.26–0.79, $p = 0.005$) compared to AQP4-Ab-positive patients. A higher EDSS score at onset (HR 0.86, 95% CI 0.78–0.96, $p = 0.005$) and the presence of maintenance therapy (HR 0.43, 95% CI 0.24–0.75, $p = 0.003$) were also related to a lower risk for clinical relapse (table 3).

Regarding motor outcome, MOG-Ab serostatus appeared to display a protective effect to reach a DSS score of 3.0 (HR 0.46, 95% CI 0.22–0.94, $p = 0.033$). Moreover, a higher EDSS score at onset was related to a worse outcome (HR 1.32, 95% CI 1.16–1.50, $p < 0.001$) (table 3).

We found that MOG-Ab serostatus was related to a lower risk to reach VA of 20/100 (HR 0.23, 95% CI 0.07–0.72, $p = 0.012$) as well as a higher severity at onset of symptoms (HR 1.52, 95% CI 1.12–2.05, $p = 0.007$) compared to AQP4-Ab (table 3). Kaplan-Meier estimations of time to first relapse, time to a DSS score of 3.0, and time to VA of 20/100 are depicted in figure 2.

Serum longitudinal analyses of MOG-Ab titers

Serum longitudinal samples were obtained from 24 MOG-Ab-positive patients (54 serum samples) with a median interval between first and last sample of 5.8 (IQR 3.8–14.4) months. MOG-Ab titers were higher in relapsing samples ($n = 19$, median 10,240, IQR 5,120–20,480) compared to remission samples ($n = 35$, median 1,280, IQR 1,280–5,120, $p = 0.006$) (figure e-4A, links.lww.com/WNL/A472).

Table 2 Radiologic features in MOG-Ab-positive patients with an initial abnormal brain MRI

	MOG-Ab group (n = 49)	AQP4-Ab group (n = 22)	p Value
Radiologic features, n (%)			
Predominantly cortical gray matter	8 (16.33)	1 (4.55)	0.257
Confined to brainstem and/or basal ganglia	14 (28.57)	8 (36.36)	0.511
Hazy/poorly demarcated lesions	10 (20.41)	3 (13.64)	0.741
Tumefactive lesions	5 (10.20)	2 (9.09)	0.884
Nonspecific white matter lesions	7 (14.29)	3 (13.64)	0.942
Gadolinium enhancement	6 (12.24)	5 (22.73)	0.298
Lesion location at onset, n (%)			
Bilateral	22 (44.90)	11 (54.54)	0.563
Leptomeningeal enhancement ^a	3 (6.12)	0 (0)	0.236
Juxtacortical	20 (40.82)	7 (31.82)	0.599
Deep white matter	24 (48.98)	13 (59.09)	0.455
Periventricular	13 (26.53)	6 (27.27)	0.948
U or S shape	5 (10.20)	1 (4.55)	0.658
Dawson finger	4 (8.16)	0 (0)	0.303
Corpus callosum	5 (10.20)	2 (9.09)	0.884
Thalamus ^b	9 (18.37)	0	0.031
Brainstem	18 (36.73)	13 (59.09)	0.079
Midbrain	5 (10.2)	3 (13.64)	0.672
Pons	17 (34.69)	1 (4.55)	0.007
Medulla oblongata	7 (14.29)	10 (45.45)	0.004
Area postrema	1 (2.04)	7 (31.82)	<0.001
Adjacent to 4th ventricle	11 (22.45)	3 (13.64)	0.388
Cerebellar peduncles	9 (18.37)	4 (18.18)	0.985
Cerebellum	2 (4.08)	2 (9.09)	0.397

Abbreviations: AQP4-Ab = aquaporin-4 antibodies; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies.

^a Leptomeningeal enhancement was located in brainstem in 2 patients and in the temporal parietal lobe in 1 patient.

^b Bilateral thalamic involvement was observed in 6 of 9 (66.7%) patients with thalamic affection (pulvinar affection in 5 of 6, 83.3%).

There was a trend toward a decline in MOG-Ab titer in monophasic disease ($n = 11$, Wilcoxon matched-pairs rank-sum test, $p = 0.066$) compared to those who relapsed ($n = 13$, $p = 0.664$) (figure e-4B and e-4C, links.lww.com/WNL/A472). Among patients with monophasic disease, only 2 (18.2%) became MOG-Ab seronegative, after a median follow-up of 6.07 and 6.73 months. The remainder ($n = 9$) were still MOG-Ab positive after a median follow-up of 8.2 (IQR 5.3–12.6) months.

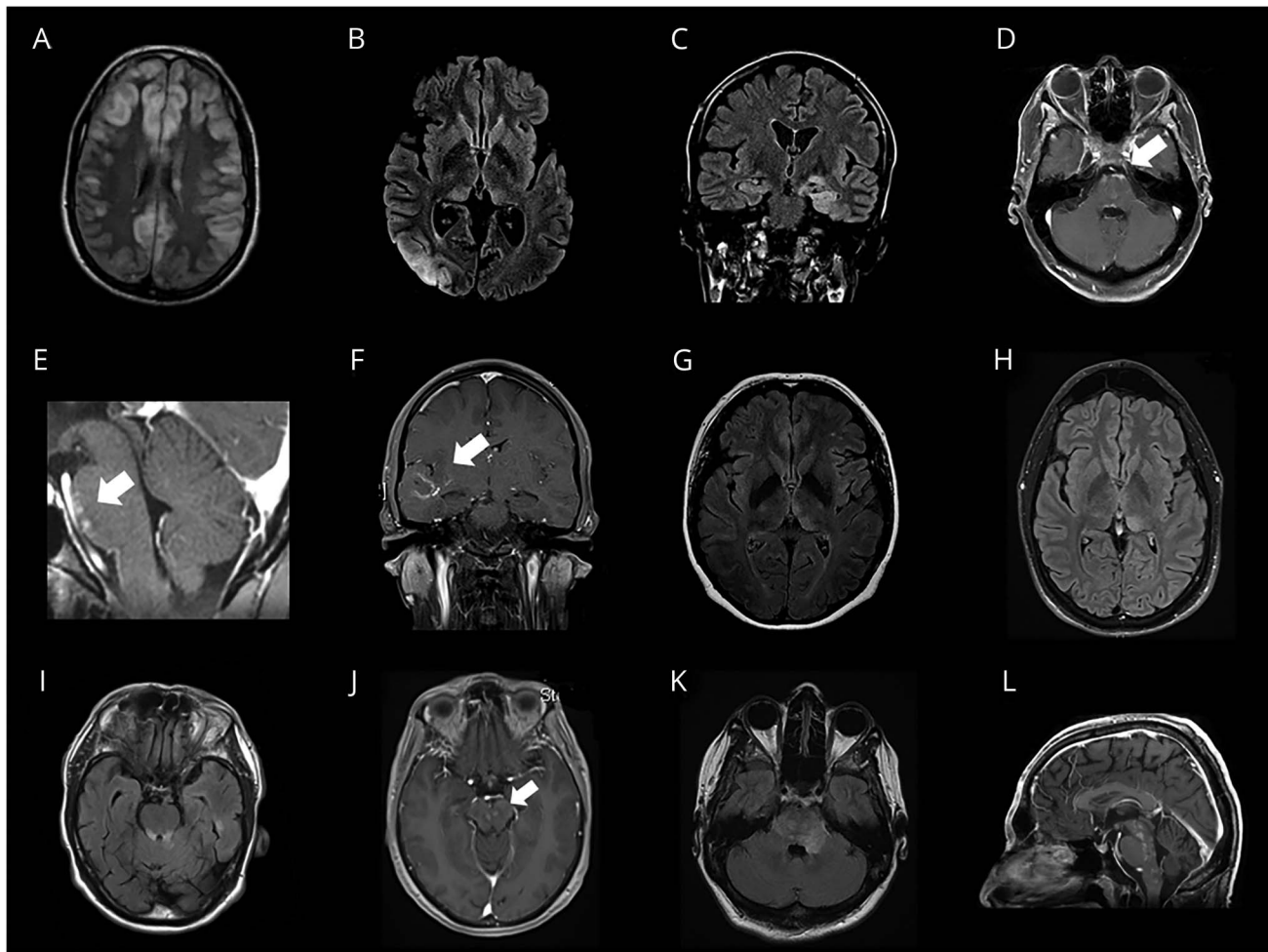
Discussion

In this large nationwide cohort of 197 adult patients with MOG-Ab, we describe a distinct phenotype, different from

AQP4-Ab NMOSD and MS. After a centralized and homogeneous antibody analysis and data collection, we observed that patients with MOG-Ab had an overall milder disease course compared to AQP4-Ab-positive patients despite a frequently relapsing disease course.

In keeping with previous reports of predominantly NMOSD clinical phenotype in adult patients with MOG-Ab-associated disease, we confirmed a high predilection for the optic nerve and the spinal cord, together making up >80% of cases.^{1–3,5,6} Brainstem was seen less frequently than in AQP4-Ab NMOSD cohorts.²⁵ Despite the predilection for the optic nerve and the spinal cord, only 19% of patients fulfilled the 2015 criteria for NMOSDs. Although the diagnostic criteria

Figure 1 Representative images of pathologic brain MRI in MOG-Ab-positive patients



(A, B) Bilateral and unilateral cortical lesions on FLAIR sequences. (C) Temporomesial cortical lesion mimicking limbic encephalitis on FLAIR sequence. (D-F) Pontine and cortical leptomeningeal gadolinium enhancement. (G, H) Thalamic lesions on FLAIR sequence. (I-K) Brainstem lesions involving the mesencephalic tegmentum and pons. (L) "Salt and pepper" brainstem pattern in CLIPPERS-like imaging. Images in (B) and (C) correspond to the same patient in different phases of disease (patient 2, table e-3, links.lww.com/WNL/A473). CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; FLAIR = fluid-attenuated inversion recovery; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies.

were designed to allow the inclusion of NMOSDs along with the presence of other antibodies,¹⁸ our study and others support that MOG-Ab-positive patients with limited forms of the disease may not fulfill them.^{1-3,5,6,26} This emphasizes the complexity of classifying patients on the basis of the clinical instead of biological phenotype.

In the present study, 45% of MOG-Ab-positive patients whose brain MRIs were evaluated at onset displayed abnormalities, in line with other findings.^{1,3,27,28} Lesions were mostly bilateral, affecting the deep white matter, and brainstem was a frequently involved structure at onset of disease. When comparing MOG-Ab- and AQP4-Ab-positive patients, we found that both groups shared common features, as recently suggested.²⁸ Nonetheless, the medulla oblongata and area postrema were more frequently affected in AQP4-Ab-positive patients, while the thalamus and pontine lesions were more often present in MOG-Ab-positive patients.

Differences in lesion location between the groups may be partially explained by a high antigen expression in specific areas.²⁹ However, brain abnormalities also occurred in areas where AQP4 expression is not particularly high,²¹ suggesting that other mechanisms could be related to lesion formation. We observed a leptomeningeal enhancement in 3 MOG-Ab-positive patients, as recently reported in AQP4-Ab-positive patients.³⁰ Our 3 cases, together with a previous case,³¹ represent a new observation in MOG-Ab-associated diseases that warrants more detailed studies.

Of note, 8 of 42 (16%) patients with abnormal brain MRIs displayed cortical involvement on imaging. Patients developed an encephalopathic picture, together with meningeal symptoms, retrograde amnesia, and seizures in some cases, symptoms not frequently reported in other demyelinating syndromes such as MS. Our finding of encephalopathic phenotype is reinforced by a recent study showing that MOG-Ab-associated

Table 3 Effects of baseline epidemiologic, clinical and CSF characteristics on time to reach a first relapse, time to reach DSS score of 3.0, and time to reach VA of 20/100

Basal variables	Time to reach a first relapse		Time to reach DSS score of 3.0		Time to reach VA of 20/100	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
MOG-Ab serostatus	0.70 (0.53–0.93), 0.013	0.45 (0.26–0.79), 0.005	0.36 (0.2–0.59), <0.001	0.46 (0.22–0.94), 0.033	0.23 (0.11–0.46), <0.001	0.23 (0.07–0.72), 0.012
Female	1.32 (0.97–1.82), 0.075	1.09 (0.59–2.01), 0.774	1.91 (1.11–3.80), 0.020	2.00 (0.80–5.00), 0.138	2.32 (1.02–5.25), 0.044	2.45 (0.49–12.24), 0.276
Age ≥60 y (referent)	—	—	—	—	—	—
Age 40–59.9 y	1.33 (0.73–2.42), 0.348		0.61 (0.34–1.10), 0.103	0.81 (0.38–1.73), 0.586	0.49 (0.13–1.78), 0.276	
Age 18–39.9 y	1.28 (0.72–2.27), 0.400		0.32 (0.17–0.58), <0.001	0.73 (0.33–1.61), 0.433	0.56 (0.17–1.88), 0.349	
White ethnicity	0.74 (0.50–1.09), 0.124		0.68 (0.40–1.18), 0.169		0.47 (0.22–0.99), 0.048	1.12 (0.28–4.42), 0.876
EDSS score at onset	0.88 (0.80–0.96), 0.006	0.86 (0.78–0.96), 0.005	1.33 (1.17–1.50), <0.001	1.32 (1.16–1.50), <0.001	1.41 (1.07–1.87), 0.014	1.52 (1.12–2.05), 0.007
CSF OCB	1.40 (0.96–2.05), 0.081	1.12 (0.62–2.02), 0.705	1.07 (0.61–1.86), 0.822		1.21 (0.36–4.04), 0.916	
CSF pleocytosis (>5 cells/mm³)	0.93 (0.67–1.28) 0.647		0.86 (0.54–1.37), 0.524		1.05 (0.45–2.41), 0.916	
Maintenance therapy	0.55 (0.36–0.82), 0.003	0.43 (0.24–0.75), 0.003	0.91 (0.46–1.80), 0.779		2.82 (1.21–6.58), 0.016	0.29 (0.03–2.74), 0.267

Abbreviations: DSS = Disability Status Scale; EDSS = Expanded Disability Status Scale; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; OCB = oligoclonal bands; VA = visual acuity.

In univariate and multivariate analyses, data are given as follows: hazard ratio (95% confidence interval), *p* value.

diseases are more frequently characterized by encephalopathy and/or seizures than AQP4-Ab-associated diseases.³² These patients fulfilled diagnostic criteria for encephalitis,³³ which may result in a diagnosis delay with treatment implications. MOG-Ab encephalitis has recently been characterized in patients with unilateral cortical affection, epilepsy, and good response to steroids,¹⁰ as well as in 1 patient with a solely bilateral frontal cortical lesions with motor deficits at onset.¹¹ None of them displayed an elevation of the myelin basic protein in CSF, and the histopathologic study from the solely biopsied patient did not show any demyelinating pattern. This suggests that other mechanisms such as cortical edema, and not pure demyelination, may be the cause.

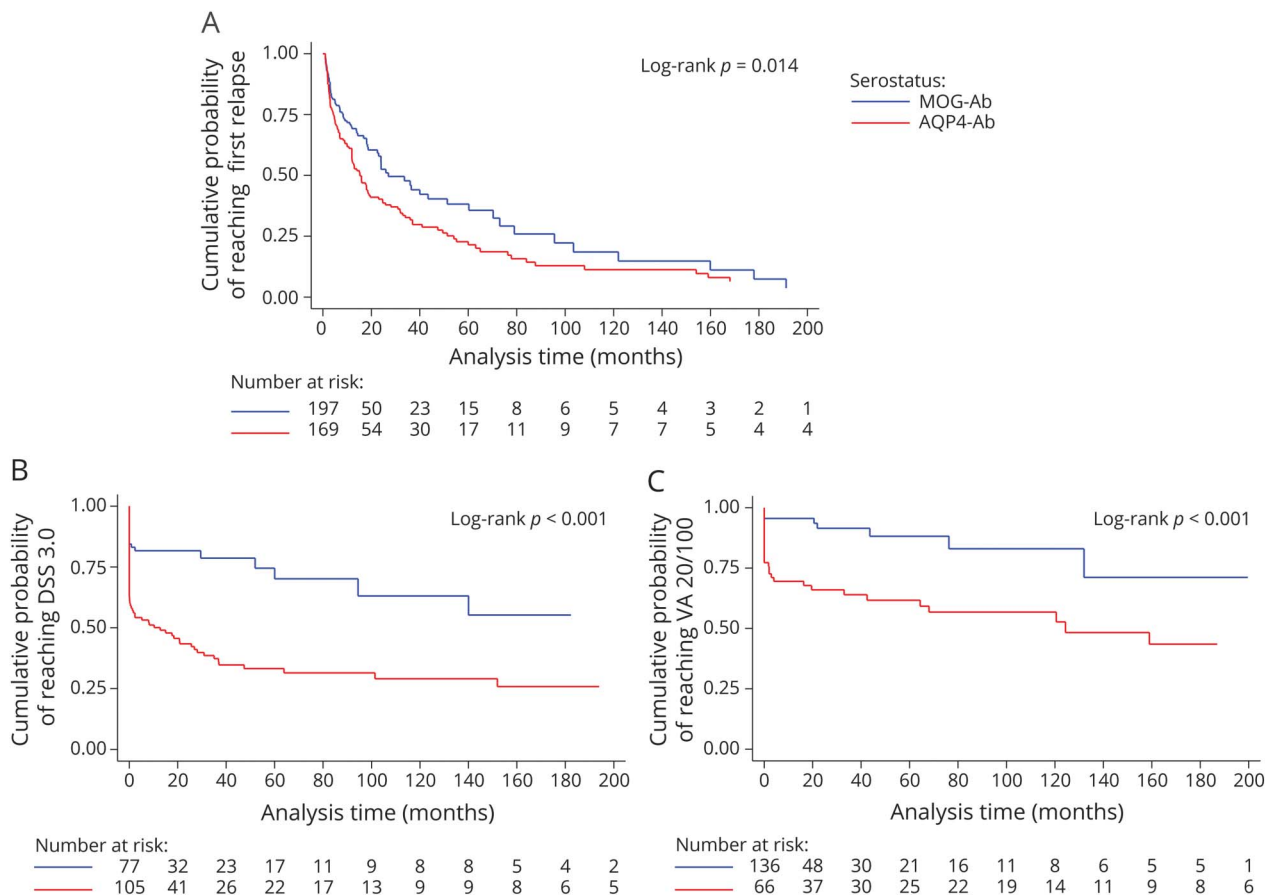
Patients with MOG-Ab-associated diseases were initially described to follow a monophasic course.^{1–3,5} However, we found here a high proportion of relapsing course, in line with others.²⁶ Even if we cannot rule out a possible selection bias in patients with monophasic course due to possible dropout, there were no differences in time to reach a first relapse between the incident and retrospective cohorts. Despite the relapsing course, MOG-Ab-positive patients exhibited a better motor and visual outcome compared to AQP4-Ab-positive patients after a first ADS. This distinction is supported by CSF findings showing evidence of specific myelin damage in MOG-Ab while both myelin and astrocyte

alteration was found in AQP4-Ab-positive patients³⁴ and experimental studies demonstrating that MOG-Ab induce a transient myelin alteration with complete recovery in mice.^{35,36} Finally, when relapsing and monophasic patients were compared, there were no differences in the proportion of patients who attained a DSS score of 3.0 or VA of 20/100, suggesting that either most of the disability is driven by the first attack or the majority of the relapses have a good recovery. Thus, although immunosuppressive agents are generally accepted to be effective in preventing relapse in AQP4-Ab-associated diseases,³⁷ prospective studies designed to evaluate efficacy in adults MOG-Ab-associated diseases are strongly recommended.

We identified a proportion of patients showing a temporal correlation between antibody titers and clinical state: higher titers at relapse compared to the remission phase and the maintenance of antibody titters in relapsing patients with time. Because we did not observe this trend across all patients (1 monophasic patient had an increase and 2 relapsing patients showed a decrease in MOG-Ab titers; figure e-4, links.lww.com/WNL/A472), these results cannot directly guide current treatment.

There are some limitations to our study. Not all patients were diagnosed at disease onset, which resulted in heterogeneity in

Figure 2 Kaplan-Meier curves



(A) Kaplan-Meier estimation of time to reach a first relapse between the MOG-Ab and AQP4-Ab groups. At 24 months after onset, 59.76% (95% CI 54.48%–67.68%) of AQP4-Ab-positive and 44.79% (95% CI 36.14%–54.48%) of MOG-Ab-positive patients developed a first relapse (log-rank $p = 0.014$). (B) Kaplan-Meier estimation of time to a DSS score of 3.0 between the MOG-Ab and AQP4-Ab groups. At 24 months after onset, 56.56% (95% CI 47.14%–66.39%) of AQP4-Ab and 18.33% (95% CI 11.29%–29.00%) of MOG-Ab-positive patients reached a DSS score of 3.0 (log-rank $p < 0.001$). (C) Kaplan-Meier estimation of time to VA of 20/100 between the MOG and AQP4-Ab groups. At 24 months, 34.01% (95% CI 23.83%–49.99%) of AQP4-Ab-positive and 8.52% (95% CI 3.94%–17.91%) of MOG-Ab-positive patients reached VA of 20/100 (log-rank $p < 0.001$). AQP4-Ab = aquaporin-4 antibody; CI = confidence interval; DSS = Disability Status Scale; MOG-ab = myelin oligodendrocyte glycoprotein antibodies; VA = visual acuity.

management and treatments with possible implication for the disease course. Because imaging and laboratory testing were done clinically, a major limitation of this study is the lack of standardized timing of MRI measures and serum samples collection. Despite the retrospective study design, we were able to standardize the diagnostic assay and the data collection across all centers, which reinforces the consistency of our results.

The present study shows that MOG-Ab-associated disease is related to a better outcome compared to AQP4-Ab NMOSDs. However, some patients displayed a poor outcome. Thus, in the near future, early identification of patients with such more severe course should be a major objective, along with a better evaluation of treatment response.

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Author contributions

Alvaro Cobo-Calvo: study concept and design, acquisition of data, analysis and interpretation, statistical analysis, writing. Anne Ruiz: laboratory analysis, critical revision of the manuscript for important intellectual content. Elisabeth Maillart, Bertrand Audoin, Helene Zephir, Bertrand Bourre, Jonathan Ciron, Nicolas Collongues, David Brassat, Francois Cotton, Caroline Papeix, Françoise Durand-Dubief, David Laplaud, Romain Deschamps, Mikaël Cohen, Damien Biotti, Xavier Aygnac, Caroline Tilikete, Eric Thouvenot, Bruno Brochet, Cecile Dulau, Thibault Moreau, Ayman Tourbah, Pierre Lebranchu, Laure Michel, Christine Lebrun-Frenay, Alexis Montcuquet, Guillaume Mathey, Marc Debouverie, Jean Pelletier, Pierre Labauge, Nathalie Derache, and Marc Coustans: acquisition of data, critical revision of the manuscript for important intellectual content. Fabien Rollot: acquisition of data, statistical analysis, critical revision of the manuscript for important intellectual content. Jérôme De Seze: acquisition of data, critical revision of the manuscript for important intellectual content. Sandra Vukusic: study concept and design, acquisition of data, interpretation, and critical revision of the manuscript for important intellectual content. Romain Marignier: study concept and design, acquisition of data, analysis and interpretation, writing.

Acknowledgment

The authors thank Prof. Philippe Cabre (Service de Neurologie, Hôpital Zobda Quitman, Fort-de-France, French West Indies) for fruitful comments and advice. The authors thank the NeuroBioTec group from Hôpital Civils de Lyon for supporting this study.

Study funding

The present study is supported by a grant from the Fondation pour l'Aide à la recherche sur la Sclérose en Plaques and a grant provided by the French State and handled by the

Agence Nationale de la Recherche within the framework of the Investments for the Future program under reference ANR-10-COHO-002 OFSEP. This work has been done with data from the OFSEP, which is supported by a grant provided by the French State and handled by the Agence Nationale de la Recherche within the framework of the Investments for the Future program under the reference ANR-10-COHO-002 OFSEP and by the Eugene Devic Foundation Against Multiple Sclerosis.

Disclosure

A. Cobo-Calvo has received grant from Fundación Alfonso Martin Escudero. A. Ruiz, E. Maillart, B. Audoin, H. Zephir, and B. Bourre report no disclosures relevant to the manuscript. J. Ciron has received consulting and lecturing fees, as well as travel grants from Biogen, Novartis, Genzyme, Teva Pharmaceuticals, Merck Serono, and Roche. N. Collongues has received honoraria for consulting or presentation from Biogen Idec, Almirall, Novartis, Merck Serono, LFB, Teva Pharma, Sanofi-Genzyme, and Roche, and is a member of the Editorial Board of the *Journal de la Ligue Française contre la Sclérose en plaques*. D. Brassat, F. Cotton, and C. Papeix report no disclosures relevant to the manuscript. F. Durand-Dubief serves on the scientific advisory board for Merck Serono and has received funding for travel and honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, Roche, and Teva. D. Laplaud and R. Deschamps report no disclosures relevant to the manuscript. M. Cohen reports participation in advisory boards for Biogen, Novartis, Roche, Merck, Teva, and Ad Scientam. D. Biotti has received consulting and lecturing fees and travel grants from Biogen Idec, Genzyme, Novartis, Merck Serono, Roche, Sanofi Aventis, and Teva Pharma. X. Aygnac reports no disclosures relevant to the manuscript. C. Tilikete has received consulting and travel grants from Biogen Idec, Novartis, Merck Serono, Santhera, and Teva Pharma. E. Thouvenot reports no disclosures relevant to the manuscript. B. Brochet reports honoraria for scientific boards and conferences from Biogen, Merck Serono, Sanofi-Genzyme, Bayer, Medday, Roche, Teva, Novartis, and Actelion. C. Dulau and T. Moreau report no disclosures relevant to the manuscript. A. Tourbah has received consulting fees and travel grants and reports institutional financial compensation for patient visits during the trial from MedDay Pharmaceuticals, as well as consulting and lecturing fees, travel grants, and research support from Biogen Idec, Sanofi-Genzyme, Novartis, Merck Serono, Teva Pharmaceuticals, and Roche. P. Lebranchu has received consulting and travel grants from Allergan. L. Michel reports no disclosures relevant to the manuscript. C. Lebrun-Frenay reports honoraria for scientific boards and conferences from Biogen, Sanofi Genzyme, Roche, Merck, Teva, Novartis, and MedDay. A. Montcuquet has received lecturing fees and travel grants from Biogen Idec, Sanofi-Genzyme, Novartis, Merck Serono, Roche, and Teva Pharma. G. Mathey and M. Debouverie report no disclosures relevant to the manuscript. J. Pelletier has received consulting and lecturing fees, travel grants, and research support from Biogen Idec, Genzyme, Novartis,

Merck Serono, Roche, and Teva Pharma. P. Labauge, N. Derache, M. Coustans, F. Rollot, and J. De Seze report no disclosures relevant to the manuscript. S. Vukusic has received consulting and lecturing fees, travel grants, and research support from Biogen, Geneuro, Genzyme, Novartis, Merck Serono, Roche, Sanofi Aventis, and Teva Pharma. R. Marignier has received consulting and lecturing fees, travel grants, and research support from Bayer-Schering, Biogen Idec, Genzyme, Novartis, Merck Serono, Roche, Sanofi Aventis, and Teva Pharma. Go to Neurology.org/N for full disclosures.

Received October 4, 2017. Accepted in final form February 27, 2018.

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