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Alvaro Cobo-Calvo, MD, PhD ,[1,2,3] Anne Ruiz, MSc,[3] Fabien Rollot, MSc ,[4] Georgina Arrambide, MD, PhD,[2] Romain Deschamps, MD, PhD,[5] Elisabeth Maillart, MD,[6] Caroline Papeix, MD, PhD,[6] Bertrand Audoin, MD, PhD,[7] Anne Fabienne Lépine, MD,[8] Hélène Maurey, MD,[9,10] Helene Zephir, MD, PhD,[11,12] Damien Biotti, MD,[13] Jonathan Ciron, MD,[13] Francoise Durand-Dubief, MD, PhD,[1] Nicolas Collongues, MD, PhD,[14] Xavier Ayrignac, MD, PhD ,[15] Pierre Labauge, MD, PhD,[15] Pierre Meyer, MD,[16] Eric Thouvenot, MD, PhD,[17] Bertrand Bourre, MD,[18] Alexis Montcuquet, MD,[19] Mikael Cohen, MD, PhD,[20] Philippe Horello, PhD,[21] Mar Tintoré, MD, PhD,[2] Jerome De Seze, MD, PhD,[14] Sandra Vukusic, MD, PhD,[1,3,4] Kumaran Deiva, MD, PhD,[22,23] and Romain Marignier, MD, PhD,[1,3]
the NOMADMUS, KidBioSEP, and OFSEP study groups

Address correspondence to Dr Marignier, Service de Neurologie, Sclérose en Plaques, Pathologies de la Myéline et Neuro-Inflammation–Hôpital Neurologique Pierre Wertheimer, 59 boulevard Pinel, 69677 Bron cedex, France. E-mail: romain.marignier@chu-lyon.fr

From the [1]Department of Neurology, Multiple Sclerosis and Neuroinflammation, Pierre Wertheimer Neurological Hospital, Lyon Civil Hospices, Lyon, France; [2]Department of Neurology-Neuroimmunology, Multiple Sclerosis Center Catalonia, Vall d'Hebron Institute of Research, Vall d'Hebron University Hospital, Autonomous University of Barcelona, Barcelona, Spain; [3]Lyon Neuroscience Research Center, U1028 INSERM, UMR5292 CNRS, FLUID Team, Lyon, France; [4]University of Lyon, Claude Bernard University Lyon 1, Lyon Civil Hospices, EDMUS Foundation, OFSEP, Lyon Neuroscience Research Center, Lyon, France; [5]Department of Neurology, Adolphe de Rothschild Hospital Foundation, Paris, France; [6]Department of Neurology and Reference Center for Rare Inflammatory Diseases of the Brain and Bone, Pitié-Salpêtrière Hospital, Public Hospital Network of Paris, Paris, France; [7]Aix-Marseille University, Public Assistance Hospitals of Marseille, Timone Hospital, Clinical Neuroscience Center, Neurology Department, Marseille, France; [8]Pediatric Neurology Department, Timone Hospital, Public Assistance Hospitals of Marseille, Marseille, France; [9]National Referral Center for Neuroinflammatory Diseases and Pediatric Neurology Department, Public Hospital Network of Paris, Bicêtre Hospital, Le Kremlin-Bicêtre, France; [10]Department of Neuropediatrics, University of Paris-Sud, Le Kremlin-Bicêtre, France; [11]University Lille, INSERM, CHU Lille, U1172–Laboratory of Neuroinflammation and Multiple Sclerosis, Lille Neuroscience & Cognition, Lille, France; [12]Department of Neurology, SEP Resource and Competence Center, Lille, France; [13]Department of Neurology, CRC-SEP, Toulouse University Hospital, Toulouse, France; [14]Department of Neurology and Clinical Investigation Center, INSERM 1434, Strasbourg University Hospital, Strasbourg, France; [15]Department of Neurology, Montpellier University Hospital, Montpellier, France; [16]Department of Pediatric Neurology, CHU Montpellier, PhyMedExp, University of Montpellier, INSERM, CNRS, Montpellier, France; [17]Department of Neurology, Carémeau Hospital, Nimes University Hospital, Nimes, France; [18]Department of Neurology, Rouen University Hospital, Rouen, France; [19]Department of Neurology, Dupuytren Hospital, Limoges, France; [20]Department of Neurology, CRCSEP, Cote d'Azur Clinical Research Unit, Pasteur University Hospital Center 2, Nice, France; [21]Division of Immunovirology, INSERM, U1184, Center for Immunology of Viral Infections and Autoimmune Diseases, University of Paris-Sud 11, CEA, DSV/iMETI, IDMIT, Faculty of Medicine, Le Kremlin-Bicêtre, France; [22]Pediatric Neurology Department, National Referral Center for Rare Inflammatory Brain and Spinal Diseases, Public Hospital Network of Paris, University of Paris-Sud Hospitals, Bicêtre Hospital, Le Kremlin-Bicêtre, France; and [23]Center for Immunology of Viral Infections and Autoimmune Diseases, University of Paris-Sud, UMR 1184-CEA-IDMIT, Le Kremlin-Bicêtre, France

Objective: The main objective was to compare clinical features, disease course, and myelin oligodendrocyte glycoprotein (MOG) antibody (Ab) dynamics between children and adults with MOG-Ab–associated disease (MOGAD).
Methods: This retrospective multicentric, national study included 98 children and 268 adults with MOGAD between January 2014 and September 2019. Cox regression model for recurrent time-to-event data and Kaplan–Meier curves for time to antibody negativity were performed for the objectives.
Results: Isolated optic neuritis was the most frequent clinical presentation in both children (40.8%) and adults (55.9%, $p = 0.013$), and acute disseminated encephalomyelitis syndrome was more frequent in children (36.7% vs 5.6%, $p < 0.001$). Compared to adults, children displayed better recovery (Expanded Disability Status Scale ≥ 3.0 at last follow-up reached only by 10 of 97 [10.3%] vs 66/247 [26.7%], $p < 0.001$). In the multivariate analysis, adults were at higher risk of relapse than children (hazard ratio = 1.41, 95% confidence interval [CI] = 1.12–1.78, $p = 0.003$). At 2 years, 64.2% (95% CI = 40.9–86.5) of nonrelapsing children became MOG-Ab negative compared to 14.1% (95% CI = 4.7–38.3) of relapsing children (log-rank $p < 0.001$), with no differences observed in adults (log-rank $p = 0.280$).
Interpretation: MOGAD patients differ in the clinical presentation at onset, showing an age-related shift in the clinical features across age groups. Compared to children, adults have a higher risk of relapse and worse functional recovery. Finally, children with monophasic disease become MOG-Ab negative earlier than relapsing children, but this is not true in adults. Considering these differences, management and treatment guidelines should be considered independently in children and adults.

Myelin oligodendrocyte glycoprotein (MOG) antibodies (Abs) are found in patients with acquired demyelinating syndromes (ADSs), delineating a disease with distinctive features, termed MOG-Ab–associated disease (MOGAD).[1–4] The disease encompasses different clinical phenotypes with an age-dependent pattern reported, with a preponderance of brain manifestations compatible with an acute disseminated encephalomyelitis (ADEM) in younger patients,[5–10] and optic neuritis (ON) or transverse myelitis (TM) in adults.[2,3] Most studies describing features of children and adults with MOGAD have focused separately either on one or the other group,[2,4,5,7,10] and only few have directly compared both groups within the same cohort with standardized collection methods.[3,11]

Nationwide studies including both children and adults allow a more comprehensive and homogeneous understanding of MOGAD and may provide clues to some unresolved questions. First, whether the disease clinical features follow a continuum or a more drastic or dichotomous change across different age groups should be more precisely evaluated. Second, it is important to directly capture the behavior over the whole disease course in children and adults, regarding relapses and disability. Finally, the association between MOG-Ab dynamics and the disease course in children and adults should allow the selection of patients who deserve to be more closely monitored, but also help to decide whether both groups should be managed similarly.[2–5,7,8,12–16]

On the bases of these unmet needs, the main aim of the present study was to compare clinical features and disease course between children and adults in a nationwide French cohort of patients with MOGAD, and to evaluate MOG-Ab dynamics in those two groups.

Patients and Methods

Study Design and Participants

Children and adults were identified from all French tertiary hospitals participating in the KidBioSEP cohort, gathering all pediatric MOGAD cases, and the MOGADOR cohort, gathering all adult cases, between January 2014 (when MOG-Ab testing started in France) and September 2019.[2,17] Patients fulfilled all the following criteria: a clinical episode consistent with an ADS, defined by at least one acute clinical demyelinating episode of the central nervous system (CNS) persisting ≥24 hours; presence of MOG-Ab in serum detected at any point in the disease course; and ≥6 months of follow-up from the first episode.

All information from identified cases of the two cohorts was collected in a standardized evaluation form and registered in the French nationwide database for neuromyelitis optica and associated neurologic disorders (NOMADMUS), a subset of the Observatoire Français de la Sclérose en Plaques (OFSEP),[18] the French multiple sclerosis (MS) registry. Demographic (gender, age at disease onset) and clinical data such as date of relapses, clinical phenotype at onset, disability measured by Expanded Disability Status Scale (EDSS), and visual acuity (VA) within 1 month from onset were collected. Cerebrospinal fluid cell count (pleocytosis, >10/mm^3) and oligoclonal bands were also noted. Maintenance therapy starting date and treatment date of switch were collected. For the purpose of analysis, maintenance therapies were classified into 3 categories[19]: (1) classical MS disease-modifying drugs (DMDs), such as interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, cladribine, fingolimod, natalizumab, and alemtuzumab; (2) classical immunosuppressants used in auto-Ab–mediated diseases, such as azathioprine, mycophenolate mofetil, rituximab, ocrelizumab, long-term corticosteroids (≥6 months), and repeated intravenous immunoglobulin administration; and (3) other immunosuppressants, such as cyclophosphamide, methotrexate, and mitoxantrone. Choice of treatment was based upon neurologists' choice. Patients were classified into early treatment or late treatment patients when initiating treatment before or after the second demyelinating event, respectively.

Cell-Based Assay MOG-Ab Detection

MOG-Ab tests were performed by live cell-based assays in Paris (Inserm UMR 1184, Le Kremlin-Bicêtre Cedex) and Lyon (Lyon Neuroscience Research Center, Inserm UMR 1028) with the same protocols. Briefly, HEK293 cells were transfected with pEGFP-N1-hMOG plasmid. Serum samples were used at a dilution of 1:640. We used a secondary antibody allophycocyanin–goat antihuman IgG-Fcγ fragment-specific, and signal intensity evaluation was performed with flow-activated cell sorting.[20]

Statistical Analysis

Analysis 1: Descriptive Analysis and Risk of Relapse. Shapiro–Wilk test was performed to test normality of different continuous variables. A first descriptive analysis and clinical comparison between children and adults was performed using a parametric (t test or chi-squared) or nonparametric (Wilcoxon or Fisher exact) test, accordingly. Patients were stratified according to age at disease presentation in children (<18 years) or adults (≥18 years), and different subgroups were further categorized: children as <10 and ≥10 years, and adults as 18–39, 40–59, and ≥60. The thresholds in adults were chosen as an acceptable compromise between number of groups and group size. Survival curves were performed with the estimation of the cumulative event to reach a first relapse between children and adults using Kaplan–Meier method expressing 95% confidence intervals (CIs).

To assess the risk of relapse over the whole disease course in children and adults, a model for recurrent events was performed. Differing from time-to-first-event analysis, which focuses on the first relapse and ignores subsequent events, Cox regression model for recurrent time-to-event data (Andersen–Gill model) was performed.[21] This model assumes that events increase along the time line and also that events are independent of each other for a given patient. A univariate analysis was used to compare the risk of relapse between both groups. The event of interest was relapse, and patients were censored at the time of loss to follow-up or at the last clinical visit. Maintenance therapy stratified into the abovementioned 3 categories was included as a time-varying covariate in all the analyses. Based on pharmacodynamics and previous treatment experience, only treatments used for at least 6 months were included. Baseline variables with a value of $p \leq 0.20$ were included in the multivariate model. Hazard ratios (HRs) were reported with 95% CI.

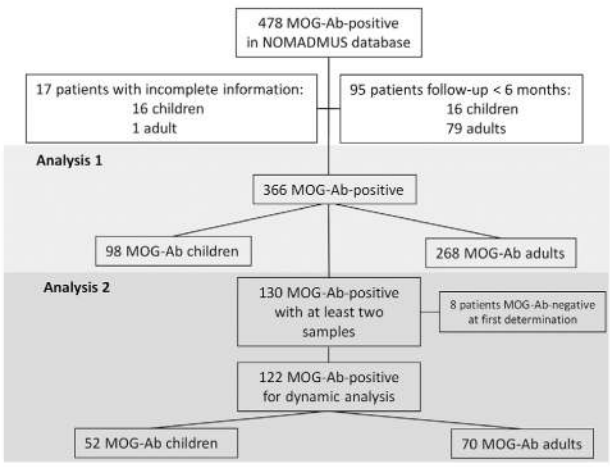

FIGURE 1: Flowchart of the patients included in the study. Ab = antibody; MOG = myelin oligodendrocyte glycoprotein.

Analysis 2: MOG-Ab Dynamics. To evaluate dynamics, delta mean fluorescence intensity ratio signal of MOG-Ab (MOG-ratio ΔMFI) was measured in patients with a minimum time elapsed between 2 samples of 4 months. Patients were classified into 3 groups according to the MOG-ratio ΔMFI: patients becoming seronegative, and patients with a decrease or an increase of the MOG-ratio ΔMFI. MOG-ratio ΔMFI was calculated as reported.[20] Kaplan–Meier survival curves were performed to compare time to antibody negativity between children and adults, according to the disease course. Comparisons were performed with the long-rank test and expressed as 95% CI.

All statistical analyses were performed using Stata 12 (64-bits; StataCorp, College Station, TX) software, and a p value < 0.05 was considered significant. Graphs were constructed with Prism (v5.0; GraphPad Software, San Diego, CA) or R-3.4.4.

Ethical Approval and Informed Consent

Data confidentiality and safety are ensured according to the recommendations of the French Commission Nationale Informatique et Libertés (CNIL). KidBIOSEP and OFSEP have received approval for storing clinical, biological, and imaging data for research purpose. This study was covered by this general approval and did not require any additional procedure, according to French law. OFSEP has been registered to clinicaltrials.gov NCT02889965.

Results

Demographic and Clinical Comparison between Adult and Children

Demographic and Phenotypical Features at Onset of Disease. At the end of the recruitment period, 478 MOG-Ab–positive patients were registered in the MOG-ADOR and KidBioSEP cohorts. Among them, 95 patients with follow-up < 6 months and 17 patients with incomplete information were excluded. Finally, 366 MOG-Ab–positive patients, 98 children and 268 adults (ratio = 1:2.7),

were included in the present study (flowchart of the patients included is depicted in Fig 1).

Among the 366 MOG-Ab–positive patients, 198 (54.1%) were female. The median (interquartile range [IQR]) age at onset was 29.9 (16.7–41.7) years. Isolated ON was the most frequent clinical phenotype at onset in both groups, but found more often in adults (150/268 [55.9%] vs 40/98 [40.8%], $p = 0.013$). ADEM was the second most frequent clinical phenotype in children (16 [36.7%]), being higher than in adults (15 [5.6%], $p < 0.001$). When stratifying by age subgroups, 24 (53.3%) and 12 (26.7%) of the 45 children aged <10 years started with ADEM and isolated ON in comparison with 12 (22.6%) and 28 (52.8%) of the 53 children aged ≥10 years, respectively ($p = 0.003$ and $p = 0.013$). Such figures were even more pronounced when splitting younger children into two groups: only 2 of 19 (10.5%) aged <5 years versus 10 of 26 (38.5%) aged 5 to 9 years presented with isolated ON ($p = 0.046$), and 13 of 19 (68.4%) aged <5 years versus 11 of 26 (42.3%) aged 5 to 9 years presented with ADEM ($p = 0.131$). An age-related shift in the phenotype at disease presentation was observed across age subgroups, as patients aged 10 to 17 years were "in between" children aged <10 years and adults. Table 1 depicts baseline features according to age at onset and Table 2 according to clinical phenotype at onset.

There were no differences regarding disability (both EDSS and VA) at onset within age subgroups of children and adults respectively (data not shown). There were no differences in the median (IQR) of follow-up between both groups (3.0 [1.9–6.1] vs 2.7 [1.4–5.9] years in children and adults, respectively; $p = 0.247$).

Disability at Last Follow-up. Sixty-six of 247 (26.7%) adults displayed an EDSS ≥ 3.0 at last follow-up compared to 10 of 97 (10.3%) children ($p = 0.001$). Among patients with at least 1 episode of ON over the whole disease course in which the VA was collected at last follow-up, 21 of 167 (12.6%) adults had a VA ≤ 0.2 compared to 2 of 48 (4.2%) children ($p = 0.069$).

Stratifying by clinical phenotypes at onset, 19 of 153 (12.4%) adults starting with ON (isolated ON or combined ON and TM) had VA ≤ 0.2 at last follow-up compared to 2 of 42 (4.7%) children ($p = 0.156$). When starting with myelitis (isolated TM or combined ON and TM), 35 of 83 (42.2%) adults showed an EDSS ≥ 3.0 at last follow-up in contrast to 3 of 16 (18.8%) children ($p = 0.070$). Such differences were more pronounced when starting with ADEM; 5 of 14 (35.7%) adults displayed an EDSS ≥ 3.0 at last follow-up when compared with 3 of 36 (8.3%) children ($p = 0.018$).

Treatment Characteristics. Maintenance therapy was started in 42 (42.8%) children compared to 184 (68.7%) adults at any time ($p < 0.001$; see Table 1). As first-line treatment, children and adults initiated similarly classical immunosuppressants used in auto-Ab–mediated diseases (33 [78.6%] vs 162 [88%], respectively; $p = 0.134$) and other immunosuppressants (1 [2.4%] vs 8 [4.4%], respectively; $p = 1.0$). However, children (8 [19.1%]) initiated MS-DMDs more frequently than adults (14/184 [7.6%]), $p = 0.039$).

When comparing baseline features, treated were older than nontreated children (median [IQR] 12.4 [6.7–15.7] years vs 9.2 [4.7–13.3], $p = 0.030$). In adults, 22 of 78 (28.2%) treated patients had an initial EDSS ≥ 6.0 compared to none of the nontreated group ($p < 0.001$). Moreover, a higher proportion of treated (57/171 [33.3%]) had an EDSS ≥ 3.0 at last follow-up compared to 9 of 76 (11.8%) nontreated adult patients ($p < 0.001$).

Characteristics of children and adults according to early or late treatment are shown in Table 3.

Disease Course in Children and Adults

Risk of Relapse in the Whole Cohort. In total, other than the index events, 493 subsequent demyelinating relapses were registered with a median (IQR) number of relapses of 2 (1–4). Fifty-two children (53.1%) and 150 (55.9%) adults had at least 1 recurrence, respectively ($p = 0.637$). The two groups did not differ in the mean annualized relapse ratio (ARR; $p = 0.219$). At 2 years, 38.6% (95% CI = 29.3–49.8) of children and 41.5% (95% CI = 35.4–48.2) of adults reached a first relapse (log-rank $p = 0.215$). Figure 2 shows recurrences along the disease course according to treatment in the whole cohort.

In the univariate analysis, adults had a 35% increase in the recurrence risk over the whole disease course in comparison with children (HR = 1.35, 95% CI = 1.09–1.67, $p = 0.005$; data not shown). When stratifying by age subgroups, patients aged 18 to 39 years were at higher risk for further relapses (HR = 1.44, 95% CI = 1.09–1.92, $p = 0.011$) than children younger than 10 years. No differences were observed among the remaining groups (Table 4).

In the multivariate analysis and after including treatment as a time-dependent covariate, patients aged 18 to 39 years were still at higher risk of relapse (HR = 1.65, 95% CI = 1.21–2.25, $p = 0.002$) than the reference group (children aged <10 years). Being female (HR = 1.10, 95% CI = 1.0–1.21, $p = 0.041$) and treated with an MS-DMD (HR = 2.44, 95% CI = 2.80–3.31, $p \leq 0.001$) also indicated a higher risk of relapse. By contrast, patients with an

TABLE 1. Demographics and Clinical Features in Children and Adults

Baseline Variables	Children			Adults				
	Total, n = 98	<10 Years, n = 45	10–17 Years, n = 53	Total, n = 268	18–39 Years, n = 165	40–59 Years, n = 87	≥60 Years, n = 16	p[a]
Females, n (%)	50 (51.0)	28 (62.2)	22 (41.5)	148 (55.2)	92 (55.8)	45 (51.7)	11 (68.8)	0.275
Phenotype at onset, n (%)								
ON	40 (40.8)	12 (26.7)	28 (52.8)	150 (55.9)	93 (56.4)	47 (54.0)	10 (62.5)	0.013
TM	12 (12.2)	7 (15.6)	5 (9.4)	69 (25.8)	43 (26.1)	22 (25.3)	4 (25)	0.007
ON & TM	4 (4.1)	0	4 (7.6)	19 (7.1)	10 (6.1)	8 (9.2)	1 (6.3)	0.342
BST	6 (6.1)	2 (4.4)	4 (7.6)	15 (5.6)	9 (5.5)	5 (5.8)	1 (6.3)	0.804
ADEM	36 (36.7)	24 (53.3)	12 (22.6)	15 (5.6)	10 (6.1)	5 (5.8)	0	<0.001
EDSS at onset, n (%)[b]								
<6.0	35/51 (68.6)	15/24 (62.5)	20/27 (74.1)	91/113 (80.5)	55/67 (82.1)	31/39 (79.5)	5/7 (71.4)	0.111
≥6.0	16/51 (31.4)	9/24 (37.5)	7/27 (25.9)	22/113 (19.5)	12/67 (17.9)	8/39 (20.5)	2/7 (28.6)	
VA at onset, n (%)[c]								0.173
>0.2	2/15 (13.3)	0/4 (0)	2/11 (18.2)	20/65 (30.8)	10/39 (25.6)	8/23 (34.8)	2/3 (66.7)	
≤0.2	13/15 (86.7)	4/4 (100)	9/11 (81.2)	45/65 (69.2)	29/39 (74.4)	15/24 (65.2)	1/3 (33.3)	
ARR, mean (SD)	0.23 (0.35)	0.17 (0.31)	0.28 (0.38)	0.35 (0.58)	0.39 (0.62)	0.31 (0.52)	0.15 (0.27)	0.219
Oligoclonal bands, n (%)	4/72 (5.6)	1/31 (3.29)	3/41 (7.3)	19 /181 (10.5)	11/105 (10.5)	6/65 (9.2)	2/11 (18.1)	0.332
Pleocytosis, >10 cells/mm^3, n (%)[d]	23/42 (54.8)	12/18 (66.7)	11/24 (45.8)	47/141 (33.3)	31/87 (35.6)	14/45 (31.1)	2/9 (22.2)	0.018
EDSS at last FU, n (%)								0.001
≤2.5	87/97 (89.7)	40/45 (88.9)	47/52 (90.4)	181/247 (73.3)	120/153 (78.4)	52/78 (66.7)	9/16 (56.3)	
≥3.0	10/97 (10.3)	5/45 (11.1)	5/52 (9.6)	66/247 (26.7)	33/153 (21.6)	26/78 (33.3)	7/16 (43.8)	
VA at last FU, n (%)[e]								0.069
≥0.7	41/48 (85.4)	14/15 (93.3)	27/33 (81.8)	115/167 (68.9)	75/104 (72.1)	34/53 (65.2)	6/10 (60)	
0.3–0.6	5/48 (10.4)	1/15 (6.7)	4/33 (12.1)	31/167 (18.6)	20/104 (19.2)	9/53 (17.0)	2/10 (20)	
≤0.2	2/48 (4.2)	0/15 (0)	2/33 (6.1)	21/167 (12.6)	9/104 (8.7)	10/53 (18.9)	2/10 (20)	
Maintenance therapy, n (%)	42/98 (42.9)	17/45 (37.8)	25/53 (47.2)	184/268 (68.7)	115/165 (69.7)	61/87 (70.1)	8/16 (50)	<0.001
FU, median yr (range)	3.0 (0.5–53.1)	4.1 (0.6–34.4)	2.9 (0.5–53.1)	2.7 (0.5–48.3)	2.8 (0.5–48.3)	2.4 (0.5–26.1)	2.6 (0.5–10.3)	0.247

[a]Comparison between the total cohort of children and adults.
[b]EDSS at onset was evaluated within 1 month from onset of symptoms.
[c]VA at onset was collected in patients with a clinical episode of ON at onset and evaluated within 1 month from onset of symptoms.
[d]Lumbar puncture was performed within the first month after onset of symptoms.
[e]VA at last FU was collected in patients presenting at least 1 episode of ON over disease course.
ADEM = acute disseminated encephalomyelitis; ARR = annualized relapse rate; BST = brainstem; EDSS = Expanded Disability Status Scale; FU = follow-up; ON = optic neuritis; SD = standard deviation; TM = transverse myelitis; VA = visual acuity.

EDSS ≥ 6.0 had a lower risk (HR = 0.54, 95% CI = 0.32–0.94, p = 0.029; see Table 4) Overall, adults had 41% more risk than children to relapse over the whole disease course (HR = 1.41, 95% CI = 1.12–1.78, p = 0.003).

Risk of Relapse according to Clinical Phenotype at Onset. When evaluating the risk of relapse stratifying by the clinical phenotype at onset, and adjusting in the multivariate analysis by gender, EDSS at onset, and maintenance therapy, there were no differences between adults and children starting with ON (HR = 1.01, 95% CI = 0.75–1.37, p = 0.938). However, adults starting with ADEM showed a higher risk for relapse over the disease course than children (HR = 1.63, 95% CI = 0.99–2.69,

TABLE 2. Baseline Features in Children and Adults according to Clinical Phenotype at Onset

	Children				Adults			
Baseline Variables	**ON, n = 40**	**TM, n = 12**	**ON & TM, n = 4**	**ADEM & BST, n = 42**	**ON, n = 150**	**TM, n = 69**	**ON & TM, n = 19**	**ADEM & BST, n = 30**
Age at onset, yr (range)	13.2 (3.9–18)	7.9 (2.6–14.6)	12.5 (10.8–14.3)	6.7 (1.4–17.3)	36.4 (18.8–73.1)	35.8 (18.3–70.3)	34.5 (19.1–63.8)	37.4 (19–76.8)
Females, n (%)	21 (52.5)	6 (50)	2 (50)	21 (50)	89 (59.3)	34 (49.3)	9 (47.3)	16 (53.3)
EDSS onset, n (%)[a]								
<6.0	22/22 (100)	0 (0)	0/1 (0)	13/22 (59.1)	68/69 (98.6)	12/27 (44.4)	4/8 (50)	7/9 (77.8)
≥6.0	0 (0)	6/6 (100)	1/1 (100)	9/22 (40.9)	1/69 (1.5)	15/27 (55.6)	4/8 (50)	2/9 (22.2)
VA at onset, n (%)[b]		—	—	—		—		—
>0.2	2/15 (13.3)				19/61 (31.2)		1/4 (25)	
≤0.2	13/15 (86.7)				42/61 (68.9)		3/4 (75)	
Oligoclonal bands, n (%)	1/35 (2.9)	1/8 (12.5)	0/2 (0)	2/27 (7.4)	5 /94 (5.3)	9/54 (16.7)	0/15 (0)	5/18 (27.8)
Pleocytosis, n (%)[c]	4/19 (21.1)	4/5 (5)	2/2 (100)	13/16 (81.3)	10/78 (12.8)	22/38 (57.9)	8/14 (57.1)	8/14 (57.1)
EDSS at last FU, n (%)								
≤2.5	37/39 (94.9)	9/12 (75)	4/4 (100)	37/42 (88.1)	113/137 (82.5)	36/64 (56.3)	12/19 (63.2)	20/27 (74.1)
≥3.0	2/39 (5.1)	3/12 (25)	0/4 (0)	5/42 (11.9)	24/137 (17.5)	28/64 (43.8)	7/19 (36.8)	7/27 (25.9)
VA at last FU, n (%)[d]								
≥0.7	31/38 (81.6)	4/4 (100)	4/4 (100)	2/2 (100)	95/137 (69.3)	6/11 (54.6)	12/16 (75)	2/3 (66.7)
0.3–0.6	5/38 (13.2)	0/4 (0)	0/4 (0)	0/2 (0)	25/137 (18.2)	3/11 (27.3)	2/16 (12.5)	1/3 (33.3)
≤0.2	2/38 (5.3)	0/4 (0)	0/4 (0)	0/2 (0)	17/137 (12.4)	2/11 (18.2)	2/16 (12.5)	0/3 (0)
Maintenance treatment, n (%)	21/40 (52.5)	6/12 (50)	1/4 (25)	14/42 (33.3)	97/150 (64.7)	52/69 (75.4)	16/19 (84.2)	20/30 (66.7)
FU, median yr (range)	2.9 (0.6–53.1)	5.5 (0.8–33.5)	2.7 (1.4–6.6)	3.1 (0.5–20.6)	2.6 (0.5–48.3)	2.7 (0.5–20.3)	2.3 (0.5–10.9)	3.6 (0.7–26.1)

[a]EDSS at onset was evaluated within 1 month from onset of symptoms.
[b]VA at onset was collected in patients with a clinical episode of ON at onset and evaluated within 1 month from onset of symptoms.
[c]Lumbar puncture was performed within the first month after onset of symptoms.
[d]VA at last follow-up was collected in patients presenting at least 1 episode of ON over disease course.
ADEM = acute disseminated encephalomyelitis; BST = brainstem; EDSS = Expanded Disability Status Scale; FU = follow-up; ON = optic neuritis; TM = transverse myelitis; VA = visual acuity.

p = 0.057) as well as adults starting with TM (HR = 2.01, 95% CI = 1.09–3.70, p = 0.024).

MOG-Ab Dynamics Analysis

One hundred thirty of 366 (35.5%) patients had at least 2 MOG-Ab detections 4 months apart. Among them, 8 of 130 (6.2%) displayed a negative result in the first sample and were excluded. Finally, 122 patients were evaluated: 52 children and 70 adults. Among the 122 participants evaluated for MOG-Ab dynamics, 43 (35.3%) became seronegative, 75 (61.5%) decreased, and 4 (3.3%) increased the MOG-ratio ΔMFI. Within groups, 34 (65.4%) of the 52 children (32 decreased and 2 increased the MOG-ratio ΔMFI) and 45 (64.3%) of the 70 adults (43 decreased and 2 increased the MOG-ratio ΔMFI) remained persistently positive (p = 1.0). Median (IQR) time from the first to the last sample was 17.5 (7.0–32.6) months in patients with persistent positivity and 22.5 (11.7–32.5) month in those becoming negative (p = 0.222).

Children with relapses were more persistently positive (22/28 [78.6%]) than those without relapses (12/24 [50%], p = 0.043). However, 23 (71.9%) of 32 relapsing adults had persistent MOG-Ab compared to 22 (57.9%) of 38 without relapses (p = 0.317).

At 2 years, 64.2% (95% CI = 40.9–86.5) of nonrelapsing children became negative compared to 14.1% (95% CI = 4.7–38.3) of relapsing patients (log-rank p < 0.001), with no differences observed in adults (log-rank p = 0.280). Finally, when directly comparing both groups, nonrelapsing children became negative earlier than adults (log-rank p = 0.062; Fig 3). Baseline features of children and adults, according to the MOG-Ab persistence or negativity, are shown in Table 5.

TABLE 3. Children and Adult Characteristics according to Treatment

	Children, n = 98				Adults, n = 268			
	Nontreated, n = 56	Treated, n = 42	Early Treatment, n = 10	Late Treatment, n = 32	Nontreated, n = 84	Treated, n = 184	Early Treatment, n = 90	Late Treatment, n = 94
Age onset, median yr, (range)	9.2 (1.4–18.0)[a]	12.4 (2.6–17.3)[a]	16.4 (3.3–16.5)	15.6 (2.6–17.3)	37.1 (18.3–76.8)	35.8 (18.5–70.8)	37.3 (18.5–70.8)	35.4 (18.8–67.1)
Females, n (%)	28 (50)	22 (52.4)	4 (40)	18 (56.3)	47 (56)	101 (54.9)	50 (55.6)	51 (54.3)
Phenotype at onset, n (%)								
ON	19 (33.9)	21 (50)	5 (50)	16 (50)	54 (64.3)	97 (52.4)	40 (44.4)	56 (59.6)
TM	6 (10.7)	6 (14.3)	0 (0)	6 (18.8)	17 (20.2)	52 (28.1)	31 (34.4)	21 (22.3)
ON&TM	3 (5.3)	1 (2.4)	0 (0)	1 (3.1)	3 (3.6)	16 (8.7)	11 (12.2)	5 (5.3)
BST	3 (5.4)	3 (7.1)	0 (0)	3 (9.4)	5 (5.9)	10 (5.4)	3 (3.3)	7 (7.45)
ADEM	25 (44.6)	11 (26.2)	5 (50)	6 (18.8)	5 (5.9)	10 (5.4)	5 (5.6)	5 (5.3)
EDSS at onset, n (%)								
<6.0	23/35 (65.7)	12/16 (75)	6/7 (85.7)	6/9 (66.7)	35/35 (100)[b]	56/78 (71.8)[b]	32/52 (61.5)[c]	24/26 (92.3)[c]
≥6.0	12/35 (34.3)	4/16 (25)	1/7 (14.3)	3/9 (33.3)	0 (0)[b]	22/78 (28.2)[b]	20/52 (38.5)[c]	2/26 (7.7)[c]
Oligoclonal bands, n (%)	3/39 (7.7)	1/33 (3.0)	0/8 (0)	1/25 (4)	4/54 (7.4)	15/127 (11.8)	6/61 (9.8)	9/66 (13.6)
Pleocytosis, n (%)[d]	9/24 (37.5)	8/18 (44.4)	2/5 (40)	6/13 (46.2)	13/39 (33.3)	34/102 (33.3)	23/64 (35.9)	11/38 (29)
EDSS at last FU, n (%)								
≤2.5	51/56 (91.1)	36/41 (87.8)	9/10 (90)	27/31 (87.1)	[b]67/76 (88.2)	[b]114/171 (66.7)	56/85 (64.7)	59/86 (68.6)
≥3.0	5/56 (8.9)	5/41 (12.2)	1/10 (10)	4/31 (12.9)	[b]9/76 (11.8)	[b]57/171 (33.3)	30/85 (35.3)	27/86 (31.4)

[a] $p < 0.05$ between nontreated and treated children.
[b] $p < 0.05$ between nontreated and treated adults.
[c] $p < 0.05$ between early and late treated adults.
[d] Lumbar puncture was performed within the first month after onset of symptoms.
ADEM = acute disseminated encephalomyelitis; BST = brainstem; EDSS = Expanded Disability Status Scale; FU = follow-up; ON = optic neuritis; TM = transverse myelitis.

Discussion

In the present study, a large-scale nationwide direct comparison between adult and children with MOGAD was performed, allowing us to identify interesting findings. We confirm that the phenotype at onset differed between groups and found an age-related shift in the clinical features across different age subgroups. In addition, adults presented a higher risk of relapse than children, and displayed a higher disability at last follow-up. Finally, contrary to adults, children with a monophasic course became MOG-Ab negative earlier than those relapsing.

In our cohort, frequency of MOGAD in adults was nearly 3-fold greater than that observed in children. The participation of most of the French centers specializing in demyelinating diseases, the data collection through homogenous standards, and the inclusion of patients within the same national central database likely reflect the real relative frequency between children and adults with MOGAD in France. It is well established that whereas MOG-Ab is present in a high proportion of children with a first episode of an ADS,[5–8] positive cases are rarely found in adults,[22,23] a finding likely explained by the lower ratio of MS diagnosis in children with demyelinating diseases. Although our study was not designed to evaluate the frequency of MOG-Ab among patients starting with a first ADS, we observed herein that the frequency of MOG-Ab in adults is probably higher than previously thought, according to recent studies.[24,25]

An age-dependent clinical phenotype is a typical feature in MOGAD characterized by an ADEM phenotype in children, whereas ON or TM is more frequently found in adults.[2,3,5–10] Interestingly, we found here that from early ages, MOGAD follows a shift in the clinical disease presentation; patients aged <10 years displayed an ADEM phenotype, which was still representative in children aged

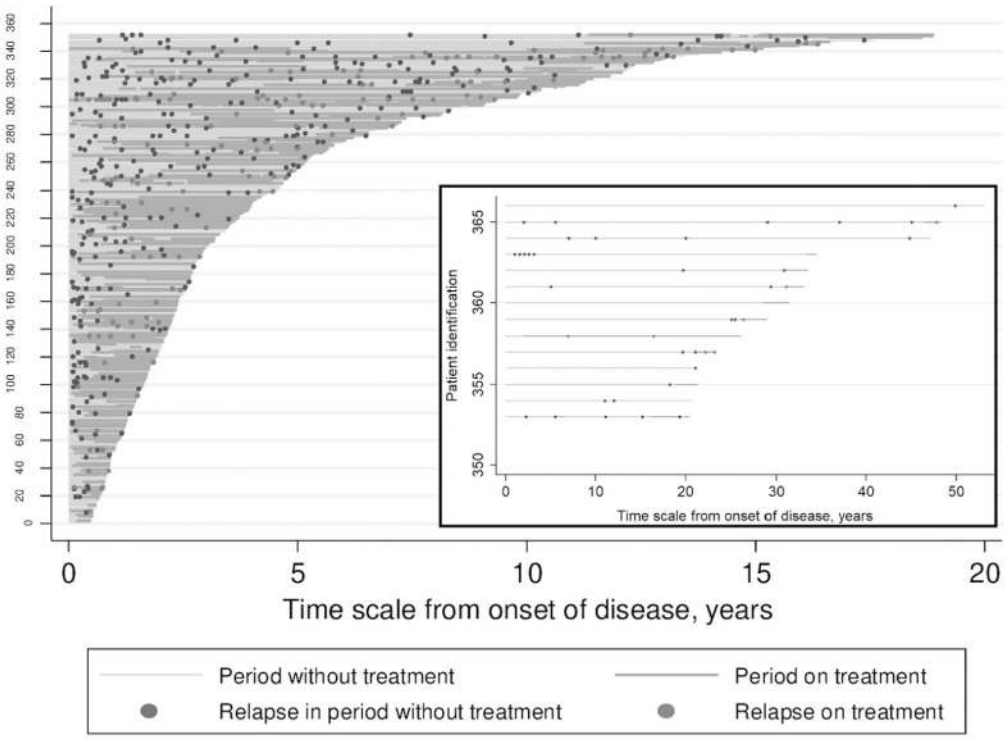

FIGURE 2: Recurrence distribution along the whole disease cohort according to treatment. *On the right side, the graphic includes 14 patients with a follow-up > 20 years.

10–18 years, but showed an abrupt decline in adult subgroups toward a marginal representation. Conversely, the optic nerve was less compromised in children, being only anecdotal in patients aged <5 years. It is worth mentioning that patients aged 10 to 18 years were shown to be a transitional group not previously described, with features "in between" the younger children (<10 years) and younger adults (18–39 years). One important question rising from this observation is the reason for such a clinical phenotype age-related shift in the involvement of CNS along the lifespan. A hypothesis that merits investigation in the basic field is a likely different structural conformation of the oligodendrocyte in which myelin sheaths would be less compact at early ages, allowing the MOG protein to be more accessible for circulating antibodies.

Apart from the clinical phenotype, there are other features showing a continuum across age subgroups. First, whereas more than one-third of children aged <10 years were highly disabled at onset, these percentages decreased with increasing age. Nonetheless, despite this higher disability at onset, children were more likely to have a substantial recovery than adults among the whole cohort after a similar follow-up. This finding was notably observed in patients starting with TM or ADEM, although a clear trend was found when considering ON. The greater ARR observed across adult subgroups, together with the better CNS capability to recover and repair damage in children, could partially explained the better recovery in children.[26] Interestingly, the lower relapse ratio in children derived from the present study contrasts with the highly active relapsing disease in MS,[27] supporting again the notion that MOGAD and MS are two different entities.

By using a specific approach to assess the risk of recurrent events,[21] we found that when considering the whole cohort, adults were at higher risk of relapse when compared with children. This increase in the risk of relapse was mainly due to differences observed in patients starting with ADEM and myelitis. This finding, together with the lower relapse rates and the better functional outcome observed in children, reflects the picture of the disease course, providing useful information to correctly design treatment guidelines. Thus, results from the present study justify the conservative treatment approach already performed by clinicians in the French clinical setting. Less restringing therapeutic measures must be adopted in adults, consistent with the idea of initiating treatment if a second relapse occurs or if there is no recovery from the index event.[28]

It is worth underlining that the present study was not specifically designed to evaluate treatment response in MOGAD, and treatment was included in the analysis as a time-dependent covariate to mitigate bias. In observational studies evaluating treatment effectiveness in MOGAD, specific statistical approaches such as propensity score

TABLE 4. Univariate and Multivariate Cox Regression Analysis for Recurrent Events (Andersen–Gill Model)

	Univariate		Multivariate	
Baseline Variables	**HR, 95% CI**	***p***	**HR, 95% CI**	***p***
Age at onset, yr				
<10	ref		ref	
10–17	0.95 (0.65–1.38)	0.775	1.17 (0.79–1.73)	0.429
18–39	1.44 (1.09–1.92)	0.011	1.65 (1.21–2.25)	0.002
40–59	1.15 (0.83–1.60)	0.403	1.35 (0.95–1.91)	0.093
≥60	0.47 (0.20–1.10)	0.083	0.55 (0.24–1.31)	0.177
Female	1.19 (0.99–1.42)	0.055	1.10 (1.0–1.21)	0.041
Phenotype at onset				
ON	ref		ref	
TM	1.17 (0.94–1.45)	0.160	1.18 (0.94–1.49)	0.151
ON & TM	0.84 (0.51–1.38)	0.500	0.85 (0.51–1.40)	0.513
BST	1.19 (0.78–1.80)	0.417	1.09 (0.72–1.66)	0.687
ADEM	1.16 (0.89–1.50)	0.272	1.20 (0.89–1.62)	0.225
EDSS at onset				
<5.5	ref	0.041	ref	0.029
≥6.0	0.57 (0.34–0.98)		0.54 (0.32–0.94)	
Pleocytosis	0.88 (0.62–1.28)	0.523		
Oligoclonal bands	0.98 (0.47–2.05)	0.972		
Maintenance therapy				
No treatment	ref		ref	
Classical MS-DMD[a]	2.69 (2.01–2.58)	<0.001	2.44 (2.80–3.31)	<0.001
Classical IS[b]	0.92 (0.73–1.17)	0.523	0.98 (0.77–1.26)	0.901
Other IS[c]	1.22 (0.57–2.59)	0.609	1.01 (0.48–2.17)	0.965

[a]Classical MS-DMDs: interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, cladribine, fingolimod, natalizumab, and alemtuzumab.
[b]Classical ISs: azathioprine, mycophenolate mofetil, rituximab, ocrelizumab, long-term corticosteroids (≥6 months), and repeated intravenous immunoglobulin administration.
[c]Other ISs: cyclophosphamide, methotrexate, and mitoxantrone.
ADEM = acute disseminated encephalomyelitis; BST = brainstem; CI = confidence interval; DMD = disease-modifying drug; EDSS = Expanded Disability Status Scale; HR = hazard ratio; IS = immunosuppressant; MS = multiple sclerosis; ON = optic neuritis; ref = reference; TM = transverse myelitis.

weighting for baseline imbalances between treated and nontreated patients should be used.[19] Therefore, although we found that classical MS-DMDs were related to a higher risk of relapse and classical immunosuppressants showed no beneficial effect, the strength of the association resulting from this covariate should not be overrated.

Two other covariates, disability at onset and sex, were associated with the risk of relapse. As in our previous study evaluating prognosis in the adult French cohort,[2] patients with higher disability at onset were at lower risk of relapse. This finding could be partially explained by the effect of chronic therapy, although a specific design to evaluate treatment response is needed, as previously discussed. Surprisingly, females were at higher risk of relapse than males in the multivariate analysis. We have no clear explanation for this finding. This effect was observed in children but not in adults when performing a post hoc analysis (children: HR = 1.54, 95% CI = 1.03–2.30 vs

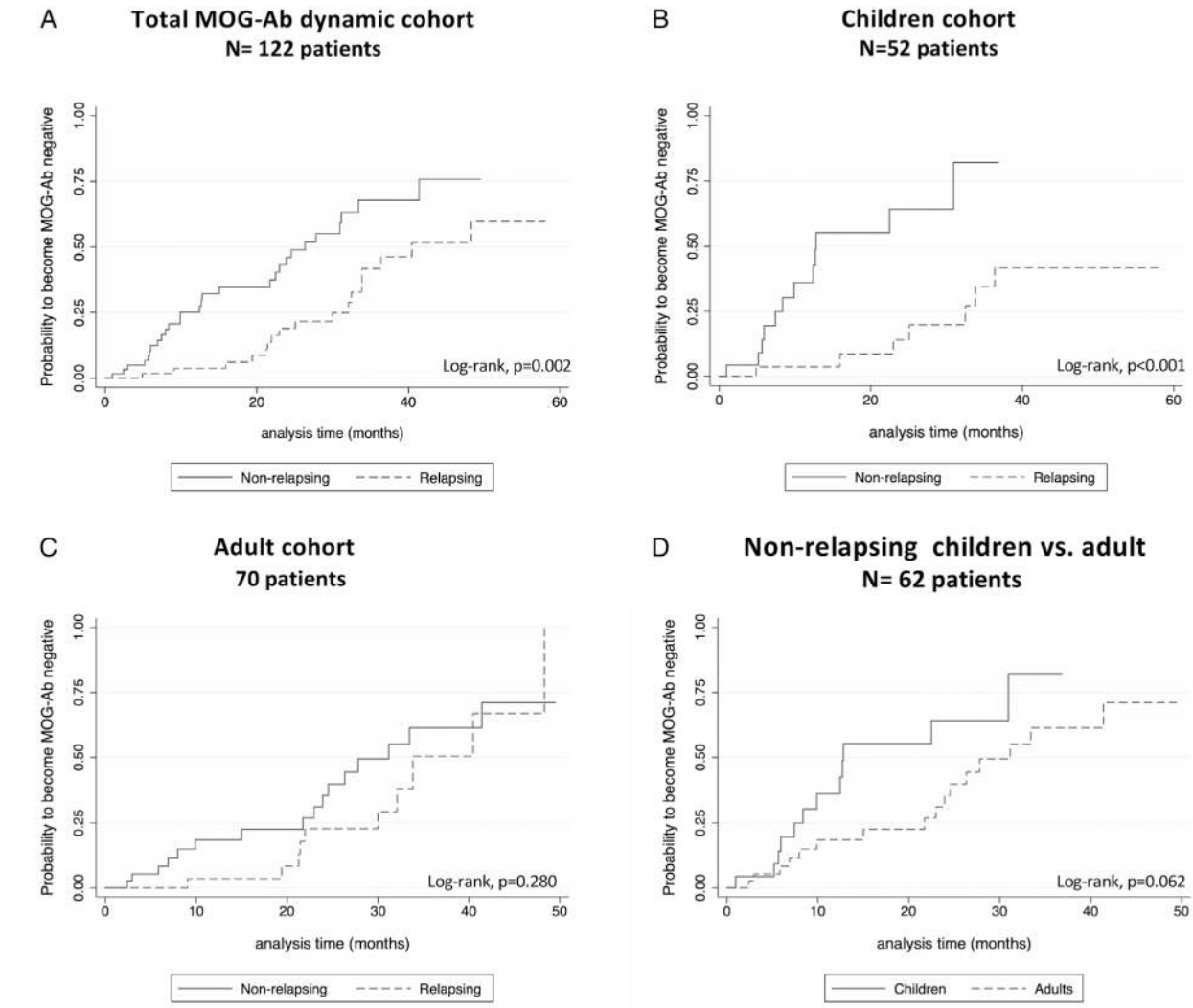

FIGURE 3: Kaplan–Meier curves of time to myelin oligodendrocyte glycoprotein (MOG)-antibody (Ab) negativity in children and adults, according to the relapse state. (A) Total cohort of 122 patients; 48.9% (95% confidence interval [CI] = 34.9–65) of nonrelapsing became negative at 2 years compared to 18.9% (95% CI = 9.8–39.5) of relapsing patients (log-rank $p = 0.002$). (B) Child cohort of 52 patients; 64.2% (95% CI = 40.9-86.5) of nonrelapsing became negative at 2 years compared to 14.1% (95% CI = 4.7–38.3) relapsing patients (log-rank $p < 0.001$). (C) Adult cohort of 70 patients; 22.8% (95% CI = 10.1–46.7) of nonrelapsing became negative at 2 years compared to 39% (95% CI = 23.9–61) relapsing patients (log-rank $p = 0.280$). (D) Children and adults nonrelapsing patients (n = 62), Kaplan–Meier comparison.

adults: HR = 1.06, 95% CI = 0.86–1.30; data not shown). Studies focusing on whether the disease course might differ depending on sex as in other demyelinating diseases such as MS deserve to be further studied.

The usefulness of antibody monitoring to foresee relapses is currently a matter of discussion, and the dynamics of MOG-Ab remains to be completely understood. An important finding was that when focusing on age groups, children with a monophasic course became negative earlier than those relapsing, whereas adults did not show the same pattern, suggesting that MOG-Ab monitoring may be more useful in the child population. These results, together with the finding that children were at lower risk of relapse than adults, support the notion that MOG-Ab dynamics and their faster antibody negativity have a major impact on the relapsing disease course.

In our study, 34.6% of children and 35.7% of adults became negative, figures that are slightly lower than the reported 52 to 57% in other studies.[7,8] In adults, specific assessment of MOG-Ab dynamics has not been performed, and data coming from mixed cohorts show 25 to 40% of antibody negativity.[3,14] These slight differences in the percentage MOG-Ab–negative patients could be explained by the longer follow-ups observed in the other studies,[7,8] but also by the application of different thresholds of positivity that may have a special impact on patients with low positive samples.[29]

TABLE 5. Baseline Features in Children and Adults according to the Myelin Oligodendrocyte Glycoprotein Antibody Dynamics

	Total Cohort, n = 122			Children, n = 52			Adults, n = 70		
	Positive, n = 45	Negative, n = 77	*p*	Positive, n = 19	Negative, n = 33	*p*	Positive, n = 26	Negative, n = 44	*p*
Age onset, median yr (range)	21.4 (1.6–73.1)	23.3 (2.6–65.7)	0.760	12.4 (1.6–17.3)	7.3 (2.6–16.4)	0.478	32.3 (19–73.1)	38.4 (18.9–65.7)	0.202
Females, n (%)	20 (44.4)	43 (55.8)	0.262	8 (42.1)	17 (51.5)	0.574	12 (46.2)	26 (59.1)	0.329
Phenotype onset, n (%)									
ON	20 (44.4)	42 (54.5)	0.349	5 (26.3)	11 (33.3)	0.758	15 (57.7)	31 (70.5)	0.307
TM	8 (17.8)	13 (16.9)	1.00	2 (10.5)	5 (15.2)	1.00	6 (23.1)	8 (18.2)	0.759
ON & TM	3 (6.7)	3 (3.9)	0.669	0	3 (9.1)	0.291	3 (11.5)	0	0.047
BST	1 (2.2)	3 (3.9)	1.000	1 (5.3)	1 (3)	1.000	0	2 (4.6)	0.526
ADEM	13 (28.9)	14 (18.2)	0.182	11 (57.9)	11 (33.3)	0.144	2 (7.7)	3 (6.8)	1.00
EDSS at onset, n (%)									
<6.0	20/29 (69)	34/39 (87.2)	0.078	9/14 (64.3)	11/16 (68.8)	1.00	11/15 (73.3)	23/23 (100)	0.018
≥6.0	9/29 (31)	5/39 (12.8)		5/14 (35.7)	5/16 (31.3)		4/15 (26.7)	0/23 (0)	
Oligoclonal bands, n (%)	4/36 (11.1)	7/55 (12.7)	0.307	3/17 (17.7)	1/21 (4.8)	0.307	1/19 (5.3)	6/34 (17.7)	0.400
Pleocytosis, n (%)[a]	21/35 (60)	12/37 (32.4)	0.033	9/14 (64.2)	7/13 (53.9)	0.704	12/21 (57.1)	5/24 (20.8)	0.016
EDSS at last FU, n (%)									
≤2.5	35/41 (85.4)	59/72 (81.9)	0.795	15/16 (93.8)	24/28 (85.7)	0.638	20/25 (80)	35/44 (79.6)	1.00
≥3.0	6/41 (14.6)	13/72 (18.1)		1/16 (6.3)	4/28 (14.3)		5/25 (20)	9/44 (20.5)	

[a]Lumbar puncture was performed within the first month after onset of symptoms.
ADEM = acute disseminated encephalomyelitis; BST = brainstem; EDSS = Expanded Disability Status Scale; FU = follow-up; ON = optic neuritis; TM = transverse myelitis.

The present work has limitations inherent to retrospective studies, although the use of standardized evaluation forms by clinicians allowed us to regularly gather in a prospective way the clinical information that could decrease this inherent bias. For instance, although EDSS was obtained in most of patients, VA was only collected in a subgroup of them, mainly because this information was difficult to access in children, leading to a small sample size when evaluating this parameter. In addition, children may not complain about VA disturbances, and it is likely that those with a severe persistent visual sequela were more closely monitored. Therefore, VA evaluation in the current retrospective setting could imply a possible bias, especially in children. In addition, the present study was not designed to evaluate cognition, a parameter that was found altered in 26% of children with MOGAD.[17] Further prospective studies focusing on cognitive impairment are urgently needed to adopt timely solutions for the affected patients. Finally, samples for MOG-Ab evaluation were not regularly collected, thus limiting survival analysis on the risk of relapse according to serostatus, as some patients may relapse before or after the period elapsed between sample assessments.

Overall, in this direct comparison between children and adults included in the same cohort, we demonstrated a progressive change in the clinical features observed along different age groups. We observed that adults displayed worse functional recovery and a higher risk of relapse than children over the whole disease course, this likely being explained by the faster MOG-Ab negativity in children. Therefore, and based on the different disease course, specific management and treatment guidelines should differentiate between children and adults.

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Author Contributions

A.C.-C., F.R., K.D., and R.M. contributed to the conception and design of the study. All authors contributed to acquisition and analysis of data. A.C.-C., K.D., and R.M. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

Nothing to report.

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