Original research

Cognition in patients with myelin oligodendrocyte glycoprotein antibody-associated disease: a prospective, longitudinal, multicentre study of 113 patients (CogniMOG-Study)

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ABSTRACT

Background Data on cognition in patients with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are limited to studies with small sample sizes. Therefore, we aimed to analyse the extent, characteristics and the longitudinal course of potential cognitive deficits in patients with MOGAD.

Methods The CogniMOG-Study is a prospective, longitudinal and multicentre observational study of 113 patients with MOGAD. Individual cognitive performance was assessed using the Paced Auditory Serial Addition Task (PASAT), the Symbol Digit Modalities Test (SDMT) and the Multiple Sclerosis Inventory Cognition (MuSIC), which are standardised against normative data from healthy controls. Cognitive performance was assessed at baseline and at 1-year and 2-year follow-up assessments. Multiple linear regression was used to analyse demographic and clinical predictors of cognitive deficits identified in previous correlation analyses.

Results At baseline, the study sample of MOGAD patients showed impaired standardised performance on MuSIC semantic fluency (mean=−0.29, 95% CI (−0.47 to −0.12)) and MuSIC congruent speed (mean=−0.73, 95% CI (−1.23 to −0.23)). Around 1 in 10 patients showed deficits in two or more cognitive measures (11%). No decline in cognition was observed during the 1-year and 2-year follow-up period. Cerebral lesions were found to be negatively predictive for SDMT (B=−8.85, 95% CI (−13.57 to −4.14)) and MuSIC semantic fluency (B=−4.17, 95% CI (−6.10 to −2.25)) test performance.

Conclusions Based on these data, we conclude that MOGAD patients show reduced visuomotor processing speed and semantic fluency to the extent that the disease burden includes cerebral lesions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous research provides inconsistent information about cognition in patients with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) from studies with small sample sizes. As a result, the prevalence and characteristics of potential cognitive deficits in MOGAD patients remain largely unknown.

WHAT THIS STUDY ADDS

⇒ This large multicentre study analysed the cognitive performance of MOGAD patients in a longitudinal setting. One in 10 patients with MOGAD (11%) showed neuropsychological deficits, particularly in visuomotor processing speed and semantic fluency. Cerebral lesions were found to be an important predictor of these cognitive deficits.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study is the first to provide a detailed cognitive profile of patients with MOGAD with the aim to better understand the disease burden in MOGAD, better address rehabilitative needs and identify potential neuropsychological endpoints for future treatment trials.

INTRODUCTION

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an autoimmune disease of the central nervous system (CNS) associated with the presence of myelin oligodendrocyte glycoprotein IgG (MOG-IgG) antibodies. The clinical presentation of MOGAD includes optic

neuritis, transverse myelitis, brainstem or cerebellar syndromes and different forms of encephalitis.[1 2]

Although clinical characteristics have been increasingly analysed in recent years, very few studies have examined the cognitive profile of patients with MOGAD. In 2020, the E.U. paediatric MOG consortium consensus noted that until then, no studies had investigated cognitive deficits in paediatric patients in a structured fashion.[3] At present, mainly observational studies on clinical characteristics of MOGAD without systematic cognitive testing exist, which report very heterogeneous results regarding the participants' cognitive performance. In studies including MOGAD patients with various disease manifestations, cognitive deficits were detected in 4%–26% of the study sample.[4–13] In contrast, three observational studies that exclusively analysed MOGAD patients with acute disseminated encephalomyelitis (ADEM) reported cognitive deficits in 40%–50% of the participants.[9 14 15] The hypothesis on cognitive performance being strongly associated with the disease manifestation is also supported by a multinational study from 2018. Among 102 children with relapsing MOGAD, cognitive deficits occurred in 30% of ADEM patients, whereas no participant with relapsing optic neuritis was reportedly affected by impaired cognition.[8] However, it should be noted that no information was provided about the methods of cognitive testing. Apart from the disease manifestation, age[7] and abnormalities of cranial MRI[7 8 12 16] were found to be factors associated with cognitive performance in MOGAD patients in previous research.

Only two clinical studies analysed specific cognitive domains in MOGAD patients. In 2021, a Chinese study examined cognition in 17 adults with MOGAD and identified cognitive deficits in verbal learning ability and information processing speed.[16] A Canadian study from 2022 analysed 12 children with relapsing MOGAD and found cognitive limitations in complex cognition, which were particularly attributable to the dimension of verbal reasoning.[17]

Beyond these studies with rather small sample sizes, cognitive performance of MOGAD patients has not yet been assessed in a structured fashion. Moreover, most existing studies focused on the cognition of paediatric patients and no detailed longitudinal data on cognitive changes in MOGAD are available.

The aim of this study was to systematically investigate the cognitive performance in a large sample of adult MOGAD patients in a prospective, longitudinal and multicentre study design.

METHODS
Participants
Between August 2015 and June 2022, a study sample of 122 patients (including 113 patients under 60 years of age) was recruited from 14 centres of the German Neuromyelitis Optica Study Group (NEMOS, www.nemos-net.de) registry. NEMOS centres are specialised in treating patients with neuromyelitis optica spectrum disorders (NMOSD) and MOGAD, collecting sociodemographic, clinical, radiological and laboratory data in a standardised fashion.[18 19] The enrolled patients participate in annual visits performed by physicians trained in the field of neuroimmunology. Inclusion of MOGAD patients aged 18 or older was based on the most recent diagnostic criteria at the time of study initiation with a typical clinical syndrome based on CNS demyelination, the presence of serum MOG-IgG, exclusion of red flags and exclusion of alternative diagnoses.[1] At least 95% (116/122) of the study sample also fulfilled the MOGAD consensus criteria proposed by Banwell et al.[20] Exclusion criteria

were the absence of written informed consent and the predominance of a neurological disease other than MOGAD (figure 1). For the follow-up analysis, two periods of 11–16 months and 23–28 months were chosen. Testing for MOG-IgG antibodies in serum was performed using established cell-based assays.[21]

Baseline and follow-up assessments
At baseline, 1-year follow-up and 2-year follow-up, participants were surveyed to collect sociodemographic and clinical data as well as information on immunotherapy and underwent a detailed neurological examination. Patients' disease manifestations (optic neuritis, myelitis, brainstem or cerebellar syndrome and cerebral lesions) are dichotomous variables assessed at each participating centre by project physicians trained in neuroimmunology according to published key features (see table 1 in Jarius et al[1] and key features of MOGAD in table 1 in Banwell et al[20]). Consequently, cerebral lesions are defined as the absence or presence of clinically symptomatic and/or asymptomatic demyelinating cerebral lesions reported to be associated with MOGAD.[1 20] Possible encephalopathic symptoms within 3 months prior to neuropsychological testing and tumefactive cerebral lesions were documented. The degree of disability was assessed using the Expanded Disability Status Scale (EDSS) performed by trained physicians.[22] EDSS values were only included in the analysis if assessed in a period of 7 days around the date of neuropsychological testing. Depressive symptoms were determined by the German version of the Revised Beck Depression Inventory (BDI-II).[23] BDI-II scores were interpreted as no depressive symptoms (0–8), minimal depressive symptoms (9–13), mild depressive symptoms (14–19), moderate depressive symptoms (20–28) and severe depressive symptoms (29–63).[23] Possible fatigue was measured by the Fatigue Scale for Motor and Cognitive Functions (FSMC).[24] The following cut-off values were used: mild fatigue ≥43, moderate fatigue ≥53 and severe fatigue ≥63.[24] Participants underwent different neuropsychological tests at baseline and follow-up visits, further defined below.

Neuropsychological tests
Participants underwent a set of neuropsychological tests administered by trained assessors as part of the annual visits. Different cognitive domains were tested by the 3 s Paced Auditory Serial Addition Task (PASAT),[25] the standard form of the Symbol Digit Modalities Test (SDMT)[26] and the Multiple Sclerosis Inventory Cognition (MuSIC).[27] The PASAT provides information about processing speed of participants in the auditory modality. The subject listens to 61 numbers presented orally at 3 s intervals and has to add each number to the previous one. The PASAT score is the number of correct sums given.[28] The SDMT is a simple visuomotor substitution task. The subject has 90 s to match the numbers one through nine with a set of geometric figures using a reference key. The SDMT was administered to measure processing speed with an emphasis on the visual modality.[25] The MuSIC is a test battery used for cognitive screening in German-speaking countries. The multiple cognitive domains measured by the MuSIC include episodic memory, assessed by immediate recall (of two orally presented 10-word lists) and delayed recall (of the first 10-word list) and semantic fluency (by alternating words from two categories within 60 s). An interference test is used to assess visual processing speed (congruent speed; naming 30 animal silhouettes) and inhibition (defined as the difference between incongruent speed minus congruent speed, where incongruent speed is defined as naming 30 silhouettes including incongruent descriptions written in the outline).[27] All test
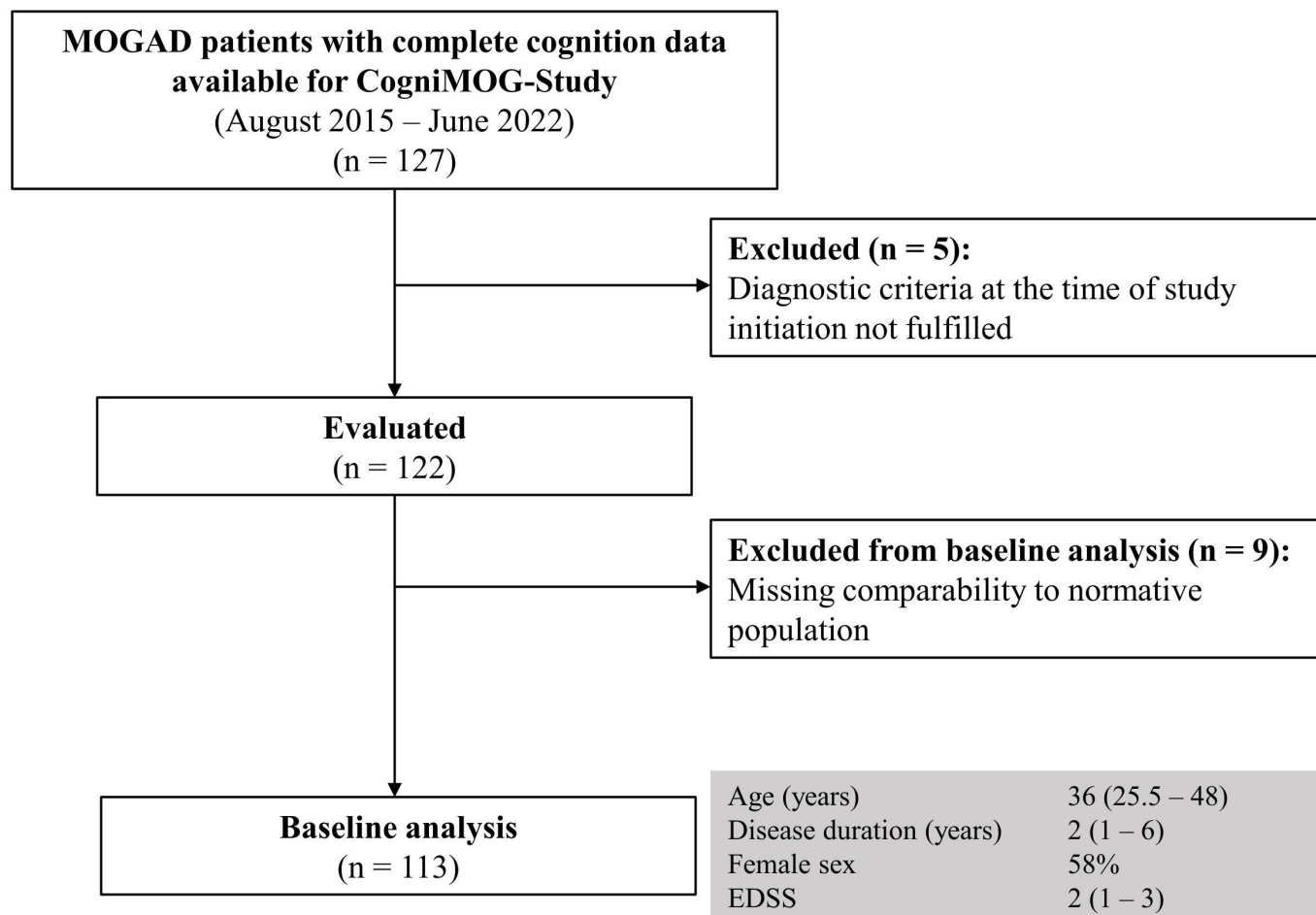
Figure 1 Selection procedure and cohort characterisation of the CogniMOG-Study. Age, disease duration and EDSS are displayed as median with IQR. Female sex is displayed as percentage. The EDSS score of 10 patients was missing. This had no impact on the representativity of the group composition. EDSS, Expanded Disability Status Scale; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease.

scores were z-standardised based on normative data of German-speaking healthy controls.[27 29] Each individual score (x) was z-transformed using the mean (m) and SD of the standardisation sample according to $z=(x-m)/SD$. Participants over 59 years of age were excluded from z-standardisation due to missing normative data of patients aged 60 (PASAT and SDMT) or 62 (MuSIC) and older (n=9). Individual z-scores of MuSIC congruent speed and MuSIC incongruent–congruent speed were multiplied by −1, so that higher values represent better test performance. The CogniMOG-Study's baseline hypothesis consisted in a significant difference between z-standardised test scores of MOGAD patients and the normative data of healthy controls. Furthermore, the fifth percentile of the normative distribution of healthy controls was used as a cut-off to identify patients with cognitive deficits in each of the domains tested.

Statistical analyses
Statistical analyses were performed in SPSS Statistics, V.27 (IBM). For descriptive statistics, categorical variables are described with frequency and percentage and continuous variables with median and boundaries of the IQR. To verify the baseline hypothesis, z-standardised test scores were evaluated by a one-sample t-test with the test value of 0. Intraindividual longitudinal analyses based on the follow-up data were performed using the Wilcoxon signed-rank test. The association between demographic and clinical variables and baseline neuropsychological test scores

was investigated. Variables of interest were sex, age, education, disease duration in years, EDSS subscale visual function, EDSS subscale motor function, FSMC and BDI-II. The Spearman's correlation coefficient was used to evaluate the relationship between continuous variables and neuropsychological test scores while Mann-Whitney tests were used to evaluate this relationship for categorical variables. Multiple linear regressions were performed to examine the combination of predictors identified in the previous analyses. In this line, eight separate regression models were performed for the eight neuropsychological tests to determine the relevance of demographic (age, education) and clinical parameters (disease manifestation: optic neuritis, myelitis, brainstem or cerebellar syndrome, cerebral lesions) for the different cognitive dimensions within these models. The parameter education was included as a dichotomous variable with 0 representing secondary school (9–10 years of school attendance) and 1 representing high school (12–13 years of school attendance). Bootstrapping with 1000 samples was performed where the assumption of normal distribution was not met (PASAT, MuSIC Immediate recall (list A), MuSIC congruent speed, MuSIC incongruent–congruent speed). All statistical tests were two tailed and statistical significance was set to $p<0.05$. Bonferroni correction for multiple comparisons was applied to p values of Spearman's correlation coefficients and regression coefficients within each separate multiple linear regression model. With exception of z-standardised test scores (exclusion of

patients >59 years of age), all patients with available cognitive data were included in the analyses listed above. Missing data are noted at the appropriate site.

RESULTS
Characteristics of the study cohort

A total of 122 patients were included (figure 1). Of these enrolled MOGAD patients, 113 were under 60 years, which is relevant for the core analyses of cognitive performance. 58% of the total cohort were female with a median age of 37 (IQR: 26–51) years, a median disease duration of 2 (IQR: 1–6) years and a median EDSS of 2 (IQR: 1–3). The disease manifestation included optic neuritis in 81/122 patients (66%), myelitis in 70/122 patients (57%), brainstem or cerebellar syndrome in 31/122 patients (25%) and cerebral lesions in 42/122 patients (34%). Neither encephalopathic symptoms within 3 months prior to neuropsychological testing nor tumefactive lesions were observed. At baseline assessment, median BDI-II score was 7 (ie, no depressive symptoms) and median FSMC score was 36 (ie, no fatigue). Participants' demographical and clinical characteristics are summarised in table 1. The follow-up analyses included data from 58 patients (first follow-up period) and 37 patients (second follow-up period) (online supplemental eFigure 1).

Baseline cognitive analyses

The baseline analyses exclusively involved patients below the age of 60 (n=113) to optimise comparability to the normative data of healthy controls. Among patients below 60 years of age, a total of 48 participants completed the PASAT, 107 the SDMT and 77 the MuSIC. MOGAD patients performed statistically discernible worse than the normative population in both MuSIC semantic fluency (mean=−0.29, 95% CI (−0.47 to −0.12)) and MuSIC congruent speed (mean=−0.73, 95% CI (−1.23 to −0.23)). Standardised test performance of the study sample was better than normative population in MuSIC immediate recall list B (mean=0.39, 95% CI (0.16 to 0.61)). In the remaining neuropsychological tests, standardised test scores of MOGAD patients did not significantly deviate from the normative population. Results of the baseline analyses are summarised in figure 2 and table 2.

Cognitive performance and deficits from baseline to follow-up

Of all participants who completed at least two neuropsychological tests, 11/99 patients (11%) showed cognitive deficits (ie, performance at or below the fifth percentile of the healthy controls' normative distribution) in two or more tested dimensions at baseline. Deficits in at least one neuropsychological test at baseline were observed in 36/113 patients (32%). The MuSIC congruent speed was the neuropsychological test with the highest proportion of patients with deficits (n=13/77, 17%) (table 3).

The intraindividual longitudinal comparison of baseline data with 1-year follow-up data showed an increase in patients' SDMT (baseline median=59.00 vs follow-up 1 median=62.00, p=0.04) and MuSIC delayed recall (list A) (baseline median=6.00 vs follow-up 1 median=7.00, p=0.002) test scores. Additionally, participants performed better at 2-year follow-up compared with baseline in SDMT (baseline median=59.00 vs follow-up 2 median=60.00, p=0.007), MuSIC immediate recall (list A) (baseline median=14.00 vs follow-up 2 median=17.00, p=0.001), MuSIC delayed recall (list A) (baseline median=6.00 vs follow-up 2 median=7.00, p=0.01) and MuSIC congruent speed (baseline median=24.50 vs follow-up 2 median=22.00, p=0.04) (online supplemental eTable 1). Accordingly, the proportion of patients with deficits in at least two neuropsychological tests decreased from baseline (11/99, 11%) to 1-year follow-up (4/49, 8%) and 2-year follow-up (0/27, 0%). A decrease was also observed in the proportion of patients with overall deficits in at least one test from baseline (36/113, 32%) to 1-year follow-up (16/55, 29%) and 2-year follow-up (5/34, 15%) (table 3).

Association of demographic and clinical variables with cognitive performance

Baseline neuropsychological test performance did not significantly correlate with disease duration, EDSS visual and motor function, FSMC or BDI-II after Bonferroni correction (online supplemental eTable 2). Likewise, there was no significant difference between male and female participants' test scores (online supplemental eTable 3).

Since participants' age (online supplemental eTable 2) and education (online supplemental eTable 4) were significantly related to test performance in certain neuropsychological subtests, these factors and the disease manifestations were included as independent variables in a multiple linear regression model. After Bonferroni correction, higher age (B=−0.35, 95% CI (−0.50 to −0.20)) and disease manifestation with cerebral lesions (B=−8.85, 95% CI (−13.57 to −4.14)) remained negative predictors for SDMT test performance, whereas higher educational level (B=7.84, 95% CI (3.57 to 12.11)) was a positive predictor for SDMT test scores. Additionally, a cerebral disease manifestation was predictive for decreased MuSIC semantic fluency test performance (B=−4.17, 95% CI (−6.10 to −2.25)) (online supplemental eTables 5-12).

DISCUSSION

The aim of this multicentre study was to determine the extent and characteristics of possible cognitive deficits in patients with MOGAD. Therefore, we investigated the frequency of patients with deficits in neuropsychological tests and analysed possible associations of sociodemographic and clinical factors with cognitive performance. We also evaluated the individual longitudinal course of patients by analysing neuropsychological test scores at one and two years of follow-up.

Based on our findings, MOGAD patients perform below average on MuSIC semantic fluency and MuSIC congruent speed compared with normative data from healthy controls. Impairment in these subtests indicates deficits in verbal fluency, mental set shifting and information processing speed.[27] On the other hand, participants' visual processing speed, as tested by the SDMT, and auditory processing speed, as tested by the PASAT, did not differ from normative data. Additionally, our findings suggest that patients with MOGAD are not impaired in episodic memory for verbal information.

In previous studies including MOGAD patients with various disease manifestation, cognitive deficits were observed in 4 to 26% of the study participants.[4–13] In our study sample, the prevalence of cognitive deficits in MOGAD was 11% for impaired performance in at least two and 32% for impaired performance in at least one neuropsychological test. Since none of the cited studies were conducted with systematic cognitive testing, a direct comparison with our study is difficult.[4–13] However, in studies exclusively analysing patients with ADEM manifestation, more participants (40%–50%) experienced cognitive deficits compared with the CogniMOG-Study.[9 14 15] It must be emphasised that the present study sample did not include any patients

Table 1 Sample characteristics

	MOGAD patients (n=122)		MOGAD patients <60 years (n=113)	
	Available n	Median (IQR), unless %	Available n	Median (IQR), unless %
Demographic characteristics				
Age (years)	122	37 (26–51)	113	36 (25.5–48)
Female (%)	71	58%	66	58%
Education	103		95	
Secondary school (%) (9–10 years of school attendance)	49	48%	46	48%
High school (%) (12–13 years of school attendance)	54	52%	49	52%
Clinical characteristics*				
Optic neuritis (%)	81	66%	74	65%
Myelitis (%)	70	57%	67	59%
Brainstem or cerebellum (%)	31	25%	29	26%
Cerebral lesions (%)	42	34%	40	35%
Disease duration (years)	122	2 (1–6)	113	2 (1–6)
EDSS				
EDSS baseline	112	2 (1–3)	103	2 (1–3)
EDSS follow-up period 1	48	2 (1–3.5)	46	2 (1–3.5)
EDSS follow-up period 2	26	2 (1–3.5)	24	2 (1–3.5)
EDSS motor functional system score	99	0 (0–1)	93	0 (0–1)
EDSS visual functional system score	99	0 (0–1)	93	0 (0–1)
Time interval since last relapse, months	105	6 (2–14.5)	98	5.5 (2–13)
Current immunotherapy (patients); %†	73	60%	68	60%
Current immunotherapy (number of treatments)	112		106	
Rituximab (%)	31	28%	29	27%
Steroids, oral (%)	31	28%	29	27%
Azathioprine (%)	25	22%	24	23%
Methotrexate (%)	8	7%	8	7%
IVIG (%)	7	6%	7	7%
Mycophenolate mofetil (%)	3	3%	3	3%
Tocilizumab (%)	3	3%	3	3%
Ciclosporine A (%)	1	1%	1	1%
Cyclophosphamide (%)	1	1%	1	1%
Interferon beta (%)	1	1%	1	1%
Other (%)	1	1%		
Psychopathological characteristics				
Depressive symptoms, BDI-II total	70	7 (1–14)	64	7 (1–14)
None (%)	41	59%	36	56%
Minimal (%)	10	14%	10	16%
Mild (%)	12	17%	11	17%
Moderate (%)	5	7%	5	8%
Severe (%)	2	3%	2	3%
Fatigue, FSMC total	67	36 (24–62)	62	37 (26–62)
None (%)	37	55%	34	55%
Mild (%)	5	8%	4	6%
Moderate (%)	9	13%	9	15%
Severe (%)	16	24%	15	24%

*69 patients (57% of all patients) and 66 patients < 60 years (58% of patients < 60 years) suffered from more than one disease manifestation.
†Immunotherapy within 90 days before the survey. 21 patients (17% of all patients) and 20 patients < 60 years (18% of patients < 60 years) were treated with more than one immunotherapy. The percentage values refer to the number of treatments performed.
BDI-II, Beck Depression Inventory-II; EDSS, Expanded Disability Status Scale; FSMC, Fatigue Scale for Motor and Cognitive Functions; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease.

z-score (mean and 95% CI)
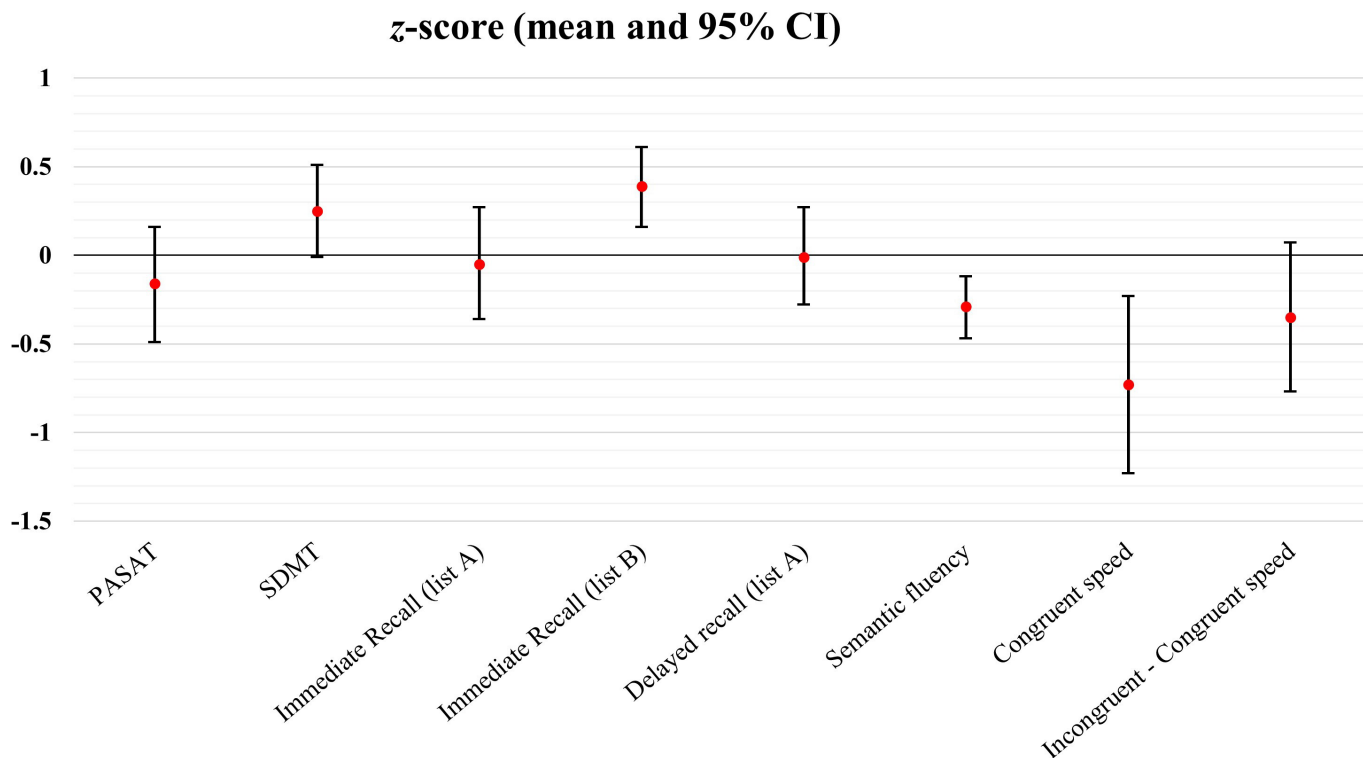
Figure 2 Mean z-scores of neuropsychological tests at baseline (patients <60 years). PASAT, Paced Auditory Serial Addition Task; SDMT, Symbol Digit Modalities Test.

with current ADEM manifestation at the time of neuropsychological testing.

Accordingly, it can be assumed that cognitive deficits in MOGAD are still rare but may mainly affect the speed of information processing, with an emphasis on the verbal dimension. These deficits are consistent with a previous observational study reporting impaired verbal reasoning in paediatric MOGAD, as semantic fluency and congruency speed cover similar cognitive dimensions.[17] Another study reported impaired verbal learning ability in adult MOGAD patients, which contrasts with the findings of the present CogniMOG study, as we did not find deficits in either immediate or delayed recall.[16]

Moreover, cognitive deficits of the MOGAD study sample mostly align with those of NMOSD patients in the recently published CogniNMO-Study, which was dedicated to cognition in NMOSD using an analogue study design.[30] In line with the cognitive profile of MOGAD patients, the CogniNMO-Study reported impaired information processing speed measured by MuSIC in NMOSD patients. Interestingly, both MOGAD patients and NMOSD patients scored slightly above the normative population in the MuSIC immediate recall (list B), which measures the episodic memory of verbal information. This might be attributable to differences in the group composition between the normative population of this subtest and the two

Table 2 Mean z-scores of neuropsychological tests and t-test at baseline

| | MOGAD patients <60 years | | | | | | |
| | | | | | 95% CI | | |
	Available n	M (SD)	t	df	LL	UL	P value
PASAT	48	−0.16 (1.13)	−1.00	47	−0.49	0.16	0.32
SDMT	107	0.25 (1.37)	1.89	106	−0.01	0.51	0.06
MuSIC							
Immediate recall (list A)	82	−0.05 (1.45)	−0.29	81	−0.36	0.27	0.77
Immediate recall (list B)	82	0.39 (1.03)	3.43	81	0.16	0.61	<0.001**
Delayed recall (list A)	82	−0.01 (1.25)	−0.04	81	−0.28	0.27	0.97
Semantic fluency	82	−0.29 (0.79)	−3.34	81	−0.47	−0.12	0.001**
Congruent speed	77	−0.73 (2.21)	−2.89	76	−1.23	−0.23	0.005**
Incongruent— Congruent speed	81	−0.35 (1.88)	−1.68	80	−0.77	0.07	0.10

**p<0.01.
LL, lower limit; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MuSIC, Multiple Sclerosis Inventory Cognition; PASAT, Paced Auditory Serial Addition Task; SDMT, Symbol Digit Modalities Test; UL, upper limit.

Table 3 Frequencies of patients with deficits in neuropsychological tests at baseline, follow-up period 1 and 2

	MOGAD patients <60 years								
	Baseline			Follow-up period 1 (11–16 months)			Follow-up period 2 (23–28 months)		
	n	deficits n	%	n	deficits n	%	n	deficits n	%
Overall deficits in ≥2 tests	99	11	11	49	4	8	27	0	0
Overall deficits in ≥1 test	113	36	32	55	16	29	34	5	15
PASAT deficits	48	4	8	21	3	14	15	0	0
SDMT deficits	107	9	8	49	4	8	30	0	0
MuSIC deficits									
Immediate recall (list A)	82	9	11	41	2	5	23	0	0
Immediate recall (list B)	82	3	4	41	1	2	24	0	0
Delayed recall (list A)	82	6	7	41	1	2	24	0	0
Semantic fluency	82	3	4	41	1	2	24	0	0
Congruent speed	77	13	17	41	6	15	22	3	14
Incongruent–Congruent speed	81	9	11	41	5	12	22	2	9

The percentage values refer to the test's subcohort.
MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MuSIC, Multiple Sclerosis Inventory Cognition; PASAT, Paced Auditory Serial Addition Task; SDMT, Symbol Digit Modalities Test.

study samples. The prevalence of cognitive deficits in at least two neuropsychological tests was lower in patients with MOGAD (11%) than in patients with NMOSD (19%). However, differences between the clinical characteristics of both study samples need to be considered, which include a lower EDSS (median=2 (MOGAD) vs median=3.5 (NMOSD)) and shorter disease duration (median=2 years (MOGAD) vs median=6 years (NMOSD)) in MOGAD patients compared with NMOSD patients. Interestingly, the neuropsychological test scores of both studies did not correlate with the disease duration of MOGAD or NMOSD patients.[30] Additionally, we did not observe impaired SDMT test performance in the MOGAD study sample, whereas NMOSD patients showed deficits in this test. Since the SDMT was significantly correlated with visual acuity in the CogniNMO-Study, this difference must be taken with caution. Together, these findings reveal further similarities but also differences between the two rare disease groups MOGAD and NMOSD in the field of cognition.[30]

Furthermore, the frequency of MOGAD patients with deficits in neuropsychological tests decreased during the 1-year and 2-year follow-up period. Potential causes for this improvement during the follow-up period have already been discussed in the literature. Particularly for the SDMT, the occurrence of a practice effect was repeatedly reported.[31 32] Further studies with a longer follow-up period are required to enable a clear distinction between specific changes in cognition and determinants such as the practice effect.

Additionally, our study replicated previous findings in terms of an association between cognition and disease manifestation.[8] Notably, a disease manifestation with cerebral lesions appears to be an important factor for reduced SDMT and MuSIC semantic fluency test performance. This association should be further addressed in specific fMRI studies to assess the target brain regions.

In this study sample, there was no association of cognitive performance and fatigue (FSMC) or depressive symptoms (BDI-II) or physical impairments, which supports that these comorbidities had no impact on neuropsychological test scores. However, the circumstance that these factors were only analysed in univariate models should be considered as a limitation of this observation. In contrast to our findings, the CogniNMO-Study identified an association between fatigue and cognitive performance in NMOSD patients. Interestingly, patients with MOGAD who were analysed in this study showed no fatigue on median. In contrast, the median fatigue in the CogniNMO-Study was of moderate severity. This is another difference between MOGAD and NMOSD warranting further investigation in studies focussing on fatigue in order to rule out possible dependencies on the group composition.[30]

A strength of our study is the large clinically well-characterised patient sample size considering the rarity of MOGAD, which was enabled by the multicentre study design. We conducted detailed questionnaires and assessments to screen for various factors that may be related to cognitive performance. However, a limitation of this study design was that not all tests were available to all participants. Since this is an ongoing study, the follow-up only contained data from patients who had already reached the respective time point. We adopted a normative study design in which z-standardisation was performed using normative data from healthy controls. Because of this standardisation, only people under the age of 60 years were included in the comparisons between MOGAD patients and healthy controls. However, in the remaining analysis, all patients were included. It is also important to consider that the collection of normative data, particularly for MuSIC, was conducted several years ago. Sociodemographic changes since the data collection may have led to differences in the group composition between MOGAD patients and the normative population. Given this background, an underestimation of the cognitive deficits in MOGAD patients cannot be completely ruled out. The participant selection procedure may be a source of potential confounding since patients with conditions such as severe encephalopathy may be unable

to attend neuropsychological testing. Thus, our findings might not be applicable to severely affected patients with MOGAD. It must be emphasised that the multiple linear regression models do not include all potential predictors of the cognitive test performance. This is attributable to the data availability, which is too sparse for a comprehensive prediction model. Nevertheless, considering the rarity of the disease, it is important to analyse all available data gathered by 14 centres. We, therefore, investigated the influence of selected factors in their interaction on cognitive performance.

CONCLUSION

This multicentre study was the first to examine the cognitive profile of adult MOGAD patients in a longitudinal setting with systematic neuropsychological testing. Every 10th patient showed deficits in two or more neuropsychological tests (11%). MOGAD patients showed impaired test performance in semantic fluency and congruent speed compared with normative data of healthy controls. Thus, the cognitive profile of MOGAD and NMOSD patients appears to be similar.[30] Notably, a disease manifestation with cerebral lesions appears to be an important predictor of reduced visuomotor processing speed and semantic fluency. These findings may help to better understand the disease burden in MOGAD, better address rehabilitative needs and identify potential neuropsychological endpoints for future treatment trials.

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