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The clinical spectrum of myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) – An observational study in a Portuguese population

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INTEGRATED MASTER'S DEGREE IN MEDICINE

THE CLINICAL SPECTRUM OF MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY-ASSOCIATED DISEASE (MOGAD) – AN OBSERVATIONAL STUDY IN A PORTUGUESE POPULATION

ORIGINAL RESEARCH ARTICLE

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ABSTRACT

Background: Myelin oligodendrocyte glycoprotein (MOG) antibody–associated disease (MOGAD) is a recently identified autoimmune demyelinating disease of the central nervous system (CNS) with a broad spectrum of presentations that frequently resemble those of other neuroinflammatory disorders. Research into delineating MOGAD's specific disease profile is still being conducted, with promising disease markers emerging.

Objective: To perform a comprehensive observational study of adult MOGAD patients followed at the Centro Hospitalar e Universitário de Coimbra (CHUC), Portugal.

Methods: This is a retrospective, observational study of adult MOGAD patients. Clinical and paraclinical data were analysed.

Results: A total of 16 patients were identified with a female to male ratio of 5:3 and a mean age at onset of 40.75 years. Disease course was monophasic in 31.3% and relapsing in 68.8% of patients. Severity at onset was variable (EDSS 1.0-4.0) with a mean EDSS of 3.0. The mean total annualised relapse rate (ARR) was 1.11 (range 0.2-6.0). At the acute episode that led to MOGAD diagnosis, 81.3% of patients had optical involvement. Unilateral and bilateral involvement was comparable (7:6) and visual acuity loss was reported in 84.6% of this patient subset. Fundus changes were detected in 100% of fundoscopic examinations carried out in this patient subgroup. None of our patients had CSF restricted oligoclonal bands. Of the 15 patients who had magnetic resonance imaging (MRI) data available, 53.3% presented optical nerve lesions with predominant involvement of the intraorbital and prechiasmal segments of the optic nerve, detected in three and five MRIs respectively.
Current optic coherence tomography (OCT) was available for 14 patients: six patients with a history of unilateral optic neuritis presented a mean retinal nerve fibre layer (RNFL) and mean ganglion cell-inner plexiform layer (GCIPL) thickness of 73µm and 67.5µm, respectively – comparable to the patient subset with a history of bilateral ON.
Megadose methylprednisolone was the most commonly used acute immunosuppressant in 100% of patients. Currently, 50% of patients are under long-term monotherapy immunosuppression and 25% are under active vigilance only, of these 75% are monophasic.
No statistically significant differences in prognoses were found when comparing patients with an initial low antibody titre (≤1:10) or a total number of acute episodes (≤3).

Conclusion: In our cohort of adult MOGAD patients the presentation was variable, with optic neuritis being the primary manifestation. Patient outcomes were generally favourable and follow-up OCT and MRI are important in monitoring disease progression. All patients achieved full disease control with their current treatment regimens.

Keywords: Myelin oligodendrocyte glycoprotein antibody-associated disease; neuromyelitis optica spectrum disorder; longitudinal extensive transverse myelitis; optic neuritis.

LIST OF ABBREVIATIONS

MOGAD – myelin oligodendrocyte glycoprotein antibody-associated disease

MOG – myelin oligodendrocyte glycoprotein

Anti-MOG IgG1 Abs – anti-myelin oligodendrocyte glycoprotein immunoglobulin G1 antibodies

NMOSD – neuromyelitis optica spectrum disorder

AQP4 – aquaporin 4

Anti-AQP4 IgG Abs – anti-aquaporin-4 immunoglobulin G antibodies

CNS – central nervous system

ON – optic neuritis

MS – multiple sclerosis

ADEM – acute disseminated encephalomyelitis

LETM – longitudinal extensive transverse myelitis

TM – transverse myelitis

CSF – cerebrospinal fluid

MRI – magnetic resonance imaging

OCT – optic coherence tomography

VA – visual acuity

GCIPL – ganglion cell-inner plexiform layer

RNFL – retinal nerve fibre layer

EDSS – Expanded Disability Status Scale

CHUC – Centro Hospitalar e Universitário de Coimbra

ARR – annualised relapse rate

LogMAR – Logarithm of the Minimum Angle of Resolution

OCBs – oligoclonal bands

EBNA - Epstein-Barr nuclear antigen

DMT – disease modifying therapy

PLEX – plasma exchange

IVIg – intravenous immunoglobulin

MMF – mycophenolate mofetil

1. INTRODUCTION

Myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) is an autoimmune demyelinating disease of the central nervous system (CNS) and is characterised by acute antibody-mediated attacks that may manifest as optic neuritis (ON), acute disseminated encephalomyelitis (ADEM), transverse myelitis (TM) and/or involve other structures including the brainstem and the conus medullaris. (1,2) Patients that we are now able to diagnose with MOGAD in previous years would potentially have been diagnosed with multiple sclerosis (MS) since both disease entities share many clinical features. Also, until 2018 when formal MOGAD diagnostic criteria were published, (3) MOGAD patients had frequently been incorrectly diagnosed with seronegative neuromyelitis optica spectrum disorder (NMOSD) patient population (4) due to a significant overlap of clinical features between the two diseases.

The turning point which led to MOGAD establishing itself as a distinct neurological disease came in 2007, when O'Connor et al (5) used cell-based assays to detect native anti-myelin oligodendrocyte glycoprotein immunoglobulin G antibodies (anti-MOG IgG1 Abs) which were predominantly present in patients with ADEM and sporadically in MS patients. The identification of this biomarker drove research into further delineating this new patient population.

Myelin oligodendrocyte glycoprotein (MOG) is a member of the immunoglobulin superfamily, making it highly immunogenic and its external location on the plasma membrane of oligodendrocytes and on the myelin sheath make it an accessible target for autoantibodies. Its functions are not yet fully understood, but it is believed to play an important role in the integrity and maintenance of the myelin sheath. (6)

The incidence and prevalence of MOGAD are also not yet fully clear since it is still a novel disease and generalised testing for patients was not available until relatively recently. However, European studies estimate the incidence to be between 1.6 and 3.4 per 1,000,000 person-years, including children. (7,8) Studies are not always concordant concerning the exact incidence between genders, (7,9) however, in contrast to NMOSD, there is a low association with concomitant connective tissue autoimmune disease. (10)

The disease course can be relapsing or monophasic, however if patient follow-up time is insufficient, patients with a relapsing course can be incorrectly categorised as monophasic and so far, no markers have been identified to help differentiate between the two. In some cases, an acute episode may be triggered by an infection or vaccination which are believed to cause disruption to the blood-brain barrier, permitting anti-MOG IgG1 Abs to enter the CNS. (11,12)

In order for a patient to be eligible for anti-MOG IgG1 testing, typically 3 criteria should be met: a compatible clinical picture, suggestive imaging and laboratory results. (3) Patients receive a formal MOGAD diagnosis upon a positive anti-MOG IgG1 titre. The timing and technique used for anti-MOG IgG1 detection is important and should ideally be carried out during acute attacks, treatment-free periods or 1-3 months after acute treatment (plasma exchange, intravenous immunoglobulin or corticosteroids). (13) It is still undetermined how the anti-MOG IgG1 titre may affect prognosis and response to treatment .

Although progress has been made to better understand MOGAD, the current scientific literature available on early detection, its progression profile, prognosis (and which markers may be used to predict it) and optimal treatment remains limited and without an international consensus on definitive diagnostic criteria, differentiating MOGAD from other similar pathologies within the spectra of demyelinating CNS diseases continues to be challenging. Furthermore, treatment choice is often currently based on a combination of severity of clinical presentation, response to (previous) treatments, sequelae from prior acute episodes, retrospective observational data and expert opinion – there are also no formal guidelines concerning glucocorticoid treatment for relapses and how/when long-term immunosuppressive therapy should be used in patients.

The aim of this research project is to carry out a detailed observational study of adult MOGAD patients followed at our centre. Clinical and paraclinical data concerning the disease's presentation, progression profile and response to acute and long-term treatment will be collected along with patient demographic data. By building an in-depth picture of this patient population, we hope to further our understanding of MOGAD's evolution and treatment so that in the future, patients can be accurately identified at earlier stages and thereby initiate appropriate treatment to favourably attenuate disease progression.

2. METHODS

2.1. Study design, setting and participants

This is a unicentre retrospective observational study conducted between December 1, 2021 and March 1, 2022 at the Neurology Department of the Centro Hospitalar e Universitário de Coimbra.

In order to participate in the study, patients needed to fulfil the following criteria: 1) >18 years of age at diagnosis; 2) MOGAD diagnosis with anti-MOG IgG1 seropositivity determined using cell-based assays. All patients identified before March 1, 2022 were included in the study which resulted in a total of 16 patients. Recruitment was carried out after obtaining informed consent and all extracted data was anonymised and inserted into a single secure electronic database specifically designed for this study.

2.2. Variables and measurement

Individual patient medical records were accessed to retrospectively collect data. Relevant information included 1) demographic data; 2) MOGAD diagnosis and number and phenotypes of acute episodes; 3) symptoms and physical examination of the baseline acute episode (defined as the acute episode that led to the determination of the patient's first anti-MOG IgG1 titre and therefore, MOGAD diagnosis). Our study focused particularly on the patients' baseline acute episodes rather than their inaugural episode since the baseline episode was the turning point that led to correct diagnosis; visual acuity was evaluated using the Ishihara test; 4) Laboratory data from the baseline acute episode, which included patient cerebrospinal fluid (CSF) results, anti-MOG IgG1 and anti-aquaporin 4 immunoglobulin G antibody (anti-AQP4 IgG) titres (determined using cell-based indirect immunofluorescence assay) and vitamin levels; 5) disease evolution and Expanded Disability Status Scale (EDSS); 6) acute and long-term treatment regimens and respective patient response (a response to treatment is considered complete if all subjective complaints are resolved and findings on the physical exam have either stabilised or resolved completely); 7) magnetic resonance imaging (MRI) results from the baseline acute episode and the latest available; 8) optic coherence tomography (OCT) results.

2.3. Statistical analysis

During the course of detailing both our patients' and MOGAD's characteristics, qualitative variables were reported using frequencies and respective percentages, while quantitative variables were summarised using the mean or median with associated range and/or standard deviation.

In order to investigate prognosis, two pertinent parameters with possible impact were identified and analysed: 1) initial anti-MOG IgG1 titre *(low initial titre if ≤1:10)* and 2) total number of acute episodes a patient suffered over their disease course *(lower total number of acute episodes if ≤3)*. Statistical analysis was conducted using Fisher's Exact Test for categorical variables and the non-parametric Mann Whitney U Test was used for continuous variables. A *p* value <0.05 was considered statistically significant. All statistical analysis was conducted using the IBM Statistical Package for Social Sciences (SPSS) software, version 25.

The annualised relapse rate (ARR) was calculated as the number of acute episodes per patient, per year during a specific time frame. Both the total ARR and the ARR after diagnosis were calculated.

Patient visual acuity after correction was expressed using the logarithm of the minimum angle of resolution (LogMAR) where the values 2.3, 2.8 and ≥3 refer to perception of hand movement, light perception and no light perception, respectively.

3. RESULTS

3.1. Patient demographics and disease presentation

The general demographic profile of our patients is summarised in table 1. In total, 16 adult patients with MOGAD were identified, with a 5:3 female to male ratio and a mean age of 47.63 years. In terms of medical history, we report one patient with concomitant autoimmune disease; one patient was diagnosed with ADEM during childhood, in close temporal association with their hepatitis B vaccination, and also suffers from motor sequelae from congenital cerebral palsy (G4+ left hemiparesis, G4 spasticity in left superior member, G2 spasticity in left inferior member and altered gait) that were not considered when evaluating acute episodes; another patient was diagnosed with chronic hepatitis B in 2019 and was also diagnosed with tuberculosis (TB) at their baseline acute episode. Finally, we also report one case of paraneoplastic MOGAD in a patient with active metastatic adenosquamous lung carcinoma. Medical records for two patients reported respiratory and gastrointestinal infection preceding the inaugural acute episode.

Table 1 also details MOGAD's general presentation where the mean age at disease onset was 40.75 years, however the age range was highly variable (21-62 years). Concerning the disease presentation in our cohort, the initial diagnoses given at the inaugural episode predominantly concerned idiopathic ON (43.8%), NMOSD (18.8%) and MS (12.5%). Some cases were atypical and therefore will be described in detail. One of the patients presented with unilateral palpebral oedema and ptosis, associated with bilateral optic neuritis. Another patient was initially diagnosed with benign intracranial hypertension due to bilateral moderate papilloedema (frisen 3) and minimal peripapillary haemorrhages on examination of the ocular fundus.

Table 1. Patient demographic profile and MOGAD presentation.

Total number of patients	**16**
Gender	
Female, *n* (%)	10 (62.5)
Male, *n* (%)	6 (37.5)
Age	
Mean, years	47.63
19-24, *n* (%)	0 (0.0)
25-44, *n* (%)	6 (37.5)
45-65, *n* (%)	8 (50.0)
66-80, *n* (%)	2 (12.5)
>80, *n* (%)	0 (0.0)
Concomitant disease	
Autoimmune	

Autoimmune thyroiditis + LADA, *n* (%)	1 (6.3)
Neoplastic or paraneoplastic	
Active metastatic adenosquamous lung carcinoma, *n* (%)	1 (6.3)
Neurological	
Congenital cerebral palsy + ADEM, *n* (%)	1 (6.3)
Infectious	
Tuberculosis + chronic hepatitis B, *n* (%)	1 (6.3)
Infection or vaccination prior to inaugural episode	
Infectious, *n* (%)	2 (12.5)
Vaccination, *n* (%)	0 (0.0)
Age at disease onset, mean (σ; min-max), years	40.75 (12.985; 21-62)
Age at diagnosis, mean (σ; min-max), years	44.75 (14.397; 22-65)
Time between disease onset and diagnosis	
Mean, years	4
<2, *n* (%), years	9 (56.3)
2-5, *n* (%), years	4 (25.0)
6-10, *n* (%), years	1 (6.3)
>11, *n* (%), years	2 (12.5)
Diagnosis given at inaugural acute episode	
Idiopathic ON, *n* (%)	7 (43.8)
NMOSD, *n* (%)	3 (18.8)
MS, *n* (%)	2 (12.5)
Brainstem syndrome with vertigo and ataxia, *n* (%)	1 (6.3)
Perimesencephalic lesion, *n* (%)	1 (6.3)
Benign intracranial hypertension, *n* (%)	1 (6.3)
Marked unilateral ptosis with ON, *n* (%)	1 (6.3)
Clinical presentation in all patient acute episodes	
Isolated optical involvement, *n* (%)	10 (62.5)
Isolated spinal involvement, *n* (%)	1 (6.3)
Isolated brainstem involvement, *n* (%)	1 (6.3)
Mixed involvement, *n* (%)	4 (25.0)

[a] These patient records did not detail the exact titre value and only referenced titre positivity.
n, number of patients; σ, standard deviation; min., minimum; max., maximum; LADA, latent autoimmune diabetes in adults; ADEM, acute disseminated encephalomyelitis; ON, optic neuritis; NMOSD, neuromyelitis optica spectrum disorder; MS, multiple sclerosis; anti-MOG IgG1, anti-myelin oligodendrocyte glycoprotein immunoglobulin G1.

Clinical data concerning MOGAD's presentation at the baseline acute episode and MOGAD's overall clinical progression profile is detailed in table 2. A relapsing disease course was identified in 11 (68.8%) patients and 5 (31.3%) patients demonstrated a monophasic disease course, defined as only one acute episode to date. We also record the most common reasons given for relapse. The highest values of the ARR at onset and ARR after diagnosis are attributed to the patient with paraneoplastic MOGAD.

At the baseline acute episode, two monophasic patients had a follow-up time of <2 years. Acute monophenotypic presentation occurred in 14 (87.5%) patients, of which 12 (75.0%) had

optical involvement. Two patients had an acute multiphenotypic presentation during their baseline episode. In the 13 patients with optical involvement, it was unilateral in 53.8% of cases. Visual field defects were identified in 84.6% of this patient subset and 84.6% also displayed a median LogMAR visual acuity of 1.51, ranging from slight VA loss (0) in one (7.7%) patient to no light perception (≥3.00) in two patients (15.4%). Dyschromatopsia level was recorded in 69.2% of patients, varying from 0/17 to 16.5/17; one patient maintained euchromatopsia (17/17). All fundoscopic examinations in patients with optical involvement detected fundus changes, with exclusive optic atrophy present in 46.2% of patients and exclusive disc oedema present in 30.8%. The ptosis identified in one patient was due to intraorbital inflammation with involvement of the elevator palpebrae superioris and the right superior rectus.

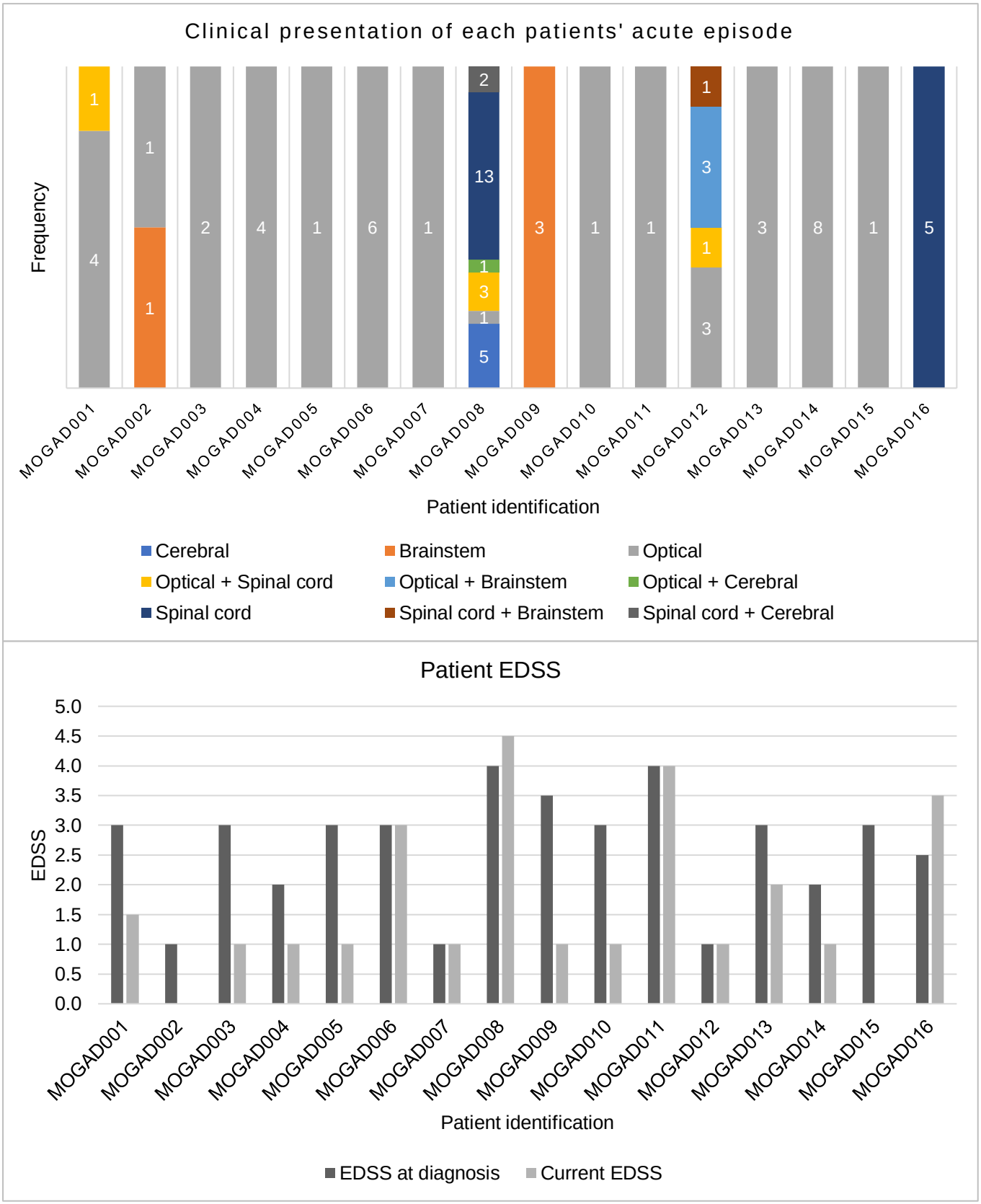
Furthermore, varying levels of paresis (no patient lost gait capacity) and altered pallasthesia were present in all patients with acute spinal cord involvement which was detected in three patients. No algic sensation changes were reported.

Regarding acute involvement of the brainstem, the patient with a purely brainstem phenotype had a single hyperintense perimesencephalic lesion which was associated with unilateral ptosis, diplopia and partial skew deviation. The second patient had a multiphenotypic presentation, and brainstem involvement manifest as ophthalmoparesis, palatal myoclonus, unilateral limb ataxia and vertigo.

The patient with acute cerebral and spinal cord involvement at the baseline episode had received a presumptive MS diagnosis 25 years before due to myelitis and optic neuritis prior relapses. The relapse that led to the diagnosis of MOGAD was characterized by cognitive decline, behavioural disturbances and worsening paraparesis.

Over disease course, 68.8% of patients had isolated optical involvement in over 50% of their acute episodes and four patients presented more than one type of acute phenotype over their disease course. The precise number and phenotypes of patient acute episodes are displayed in graph 1, along with a visual display of individual patient EDSS over disease course. Patient MOGAD011 has a medical history of congenital cerebral palsy. To note, none of the patients

reported symptomatology suggestive of area postrema syndrome (singultus, nausea and/or uncontrollable vomiting).



Graph 1. Clinical presentation of each of our patients' acute episodes and individual EDSS.

Table 2. MOGAD presentation at baseline acute episode and MOGAD progression.

Overall disease course			
Monophasic, *n* (%)			5 (31.3)
Relapsing, *n* (%)			11 (68.8)
EDSS	**At inaugural episode**	**At baseline acute episode (diagnosis)**	**Current**
Mean	3	2.63	1.66
0.0 to 2.5, *n*	2	6	12
3.0 to 3.5, *n*	10	8	2
4.0 to 4.5, *n*	2	2	2
≥5.0, *n*	0	0	0
Missing data, *n*	2	0	0
Most common reason for relapses[a] (11 patients)			
Patient did not tolerate reduction or removal of corticosteroid, *n* (% of total no. of relapsing patients)			3 (27.3)
Long-term or acute treatment ineffective, *n* (%)			3 (27.3)
Immunosuppressive treatment initiated late, *n* (%)			2 (18.2)
Unspecified, *n* (%)			3 (27.3)
Acute episodes			
Total number, mean (σ; min-max)			4.75 (5.916; 1-25)
ARR since inaugural episode, mean (σ; min-max)			1.11 (1.4082; 0.2-6.0)
ARR after diagnosis, mean (σ; min-max)			1.17 (1.5832; 0.1-6.4)
Phenotype at baseline acute episode			
1 Optical involvement, *n* (%)			12 (75.0)
2 Cerebral involvement, *n* (%)			0 (0.0)
3 Brainstem involvement, *n* (%)			1 (6.3)
4 Spinal involvement, *n* (%)			1 (6.3)
2 + 4, *n* (%)			1 (6.3)
1 + 3 + 4, *n* (%)			1 (6.3)
1. Optical involvement, *n*			**13**

Unilateral, *n* (% of total no. patients with optical involvement)	7 (53.8)
Bilateral, *n* (%)	6 (46.2)
VA loss at baseline episode, *n, %* (mean; min-max), LogMAR	11, 84.6 (1.51; 0.10-≥3.00)
Visual field defects, *n* (%)	11 (84.6)
Dyschromatopsia, *n* (mean; min-max), -/17	9 (4.8/17; 0/17-17/17)
RAPD, *n* (%)	8 (61.5)
Oculodynia, *n* (%)	6 (46.2)
Headache, *n* (%)	6 (46.2)
Ptosis[b], *n* (%)	1 (7.7)
Fundoscopy changes, *n* (%)	13 (100.0)
Atrophy, *n* (%)	6 (46.2)
Disc oedema, *n* (%)	4 (30.8)
Disc oedema + atrophy, *n* (%)	1 (7.7)
Oedema + peripapillary haemorrhages, *n* (%)	1 (7.7)
Quadrant blot haemorrhages, *n* (%)	1 (7.7)
4. Spinal cord involvement	**3**
Paresis, *n* (% of total no. patients with spinal cord involvement)	3 (100.0)
Altered sensation, *n* (%)	2 (66.7)
Spasticity, *n* (%)	2 (66.7)
Hyperreflexia, *n* (%)	2 (66.7)
Altered gait, *n* (%)	1 (33.3)
Abnormal plantar reflex present, *n* (%)	1 (33.3)
3. Brainstem involvement	**2**
Oculomotor dysfunction, *n* (% of total no. patients with brainstem involvement)	1 (50.0)
Ataxia, *n* (%)	1 (50.0)
Last cranial nerves, *n* (%)	1 (50.0)
Ophthalmoparesis, *n* (%)	1 (50.0)
Ptosis, *n* (%)	1 (50.0)
Diplopia, n (%)	1 (50.0)

Vertigo, n (%)	1 (50.0)
2. Cerebral involvement	**1**
Cognitive decline and behavioural disturbances, *n* (% of total no. patients with cerebral involvement)	1 (100.0)
Excessive sweating, *n* (%)	1 (100.0)

Paraclinical data concerning patient baseline acute episode and MOGAD's disease progression is available in table 3. Regarding the anti-MOG IgG1 testing, one patient initially had a negative titre. In the case of a patient suffering from concomitant autoimmune disease and a patient diagnosed with paraneoplastic MOGAD, the initial anti-MOG IgG1 titres were 1:32 and 1:100, respectively. Our study also identified a 1:100 titre in the patient suffering from chronic hepatitis B and TB. Of note, the highest 1:320 initial anti-MOG IgG1 titre was identified in a patient that later developed recurrent episodes of LETM. The test was repeated in 14 patients, 10 of which had the first titre available: the titre was stable in 4 patients, increased in 2 patients, decreased in 2 patients, was negative in one patient, and became positive in the initially negative patient who had performed the first test after corticotherapy,

Of the five patients with an initial 1:10 titre, one had no new titre, two maintained 1:10 at their most recent titre and in two cases, the most recent titre rose to 1:32 and 1:100. Of the three patients with an initial 1:32 titre, one maintained 1:32 on their most recent autoantibody retest, the second patient's most recent titre value fell to 1:10 and the third patient presented a negative most recent titre. In the case of the two patients with an initial titre of 1:100, one maintained 1:100 at their most recent titre and the other patient's titre fell to 1:32. There were no records of later autoantibody titres for the patient with an initial titre of 1:320. Patients who only had initial titre positivity referenced in their medical records had most recent titre levels of 1:320, 1:100, 1:32 and titre negativity. The patient with an initially negative titre underwent retesting after a month which resulted in a 1:10 titre. Their first anti-MOG IgG1 Ab test occurred within one month after a two-week 30mg of Deflazacort taper.

In our cohort, 25% of patients tested positive for the presence of antinuclear antibodies (ANA) and one patient had persistently high immunoglobulin M cardiolipin antibody titres but did not fulfil the diagnostic criteria for systemic lupus erythematosus. The CSF test results were variable, with no patient presenting oligoclonal bands (OCBs) restricted to the CSF. Only one patient had six OCBs common to both the CSF and serum.

MRIs typically conducted within one month of the baseline acute episode were available for 15 of our 16 patients. In three patients this MRI did not display any acute or suggestive abnormalities. In the remaining there was evidence of optical nerve involvement in 53.5% of MRIs and brain lesions in 40%.

To note, at the baseline acute episode, only one of our 16 patients presented with acute spinal cord lesions suggestive of longitudinal extensive transverse myelitis (LETM): the medullary image between C5-C7 displayed thickening associated with small, scattered areas of hyperintensity in T2. In addition, various intramedullary peripheral areas from the caudal section of the brainstem to D11 demonstrated contrast-enhancing lesions.

Table 3 also evidences the overall progression of MOGAD in our study cohort, particularly in relation to the imaging data. Recent MRIs were only available for 10 patients. Three patients' MRIs displayed regression of the following lesions: 1) a mesencephalic contrast-enhancing lesion, 2) hyperintensity of extraocular muscles and bilateral optic perineuritis, and 3) the third MRI demonstrated regression of scattered, hyperintense lesions in the spinal cord.

Two patient MRIs evidenced new lesions. One patient had an inflammatory, hyperintense, non-contrast enhancing lesion involving the right middle cerebellar peduncle, middle section of both cerebellar hemispheres (with greater right-side extension) and vermis which was associated with altered gait and impossible tandem gait. This patient also displayed a discrete non-contrast enhancing heterogenous intensity in the conus medullaris which had no repercussions on the spinal cord morphology and no clinical manifestation. The second patient's MRI presented a new asymptomatic 15mm hyperintense, non-contrast enhancing lesion in the periventricular white matter of the occipital region.

The simultaneous regression of a previous lesion and presence of a new asymptomatic lesion occurred in two patient MRIs. The first patient had a new small, hyperintense, non-contrast enhancing focus in the C4-C5 spinal cord and a questionable slight heterogenous hyperintensity at D2-D5. This patient's MRI also demonstrated slight spinal cord atrophy and diffuse hyperintensity without contrast enhancement. The second patient demonstrated a new hyperintense, non-contrast enhancing lesion located in the left anterior paramedian region of the medulla oblongata.

The most recently available patient OCT data is also presented in table 3. The ganglion cell-inner plexiform layer (GCIPL) and retinal nerve fibre layer (RNFL) thicknesses were very similar between the unilateral and bilateral optic neuritis groups.

Table 3. MOGAD paraclinical data associated with acute baseline episode and paraclinical disease progression.

	First anti-MOG IgG1 titre	Most recent anti-MOG IgG1 titre
1:10, *n* (%)	5 (31.3)	3 (18.8)
1:32, *n* (%)	3 (18.8)	5 (31.3)
1:100, *n* (%)	2 (12.5)	3 (18.8)
1:320, *n* (%)	1 (6.3)	1 (6.3)
"Positive"[a], *n* (%)	4 (25.0)	0 (0.0)
Negative, *n* (%)	1 (6.3)	2 (12.5)
No new titre, *n* (%)	-	2 (12.5)
Laboratory data associated with baseline acute episode		
Antibody panel[c]		
ANA, *n* positive (%; negative, missing)		4 (25; 9, 3)
Antiphospholipid Abs, *n* positive (%; negative, missing)		1 (6.3; 7, 8)
CSF		
Total protein, mean (σ; min-max), mg/dL		33.35 (14.203; 14-67)
Glucose, mean (σ; min-max), mg/dL		72.75 (28.537; 49-151)
RBC count		
<3, *n*		8
3-10, *n*		2
>10, *n*		2
Missing, *n*		4
WBC count		
<3, *n*		8
3-10, *n*		3
>10, *n*		2
Missing, *n*		3
Cytological		
Mononuclear cells, *n*		3
40% polymorphonuclear cells, 60% mononuclear cells, *n*		1

Missing, *n*	12
OCBs, *n* present (absent, missing)	1[d] (13, 2)
Vitamins	
Vitamin D, *n* deficit (normal, missing)	3 (1, 12)
Folic acid, *n* deficit (normal, missing)	2 (4, 10)
Vitamin B12, *n* deficit (normal, missing)	0 (6, 10)
EBNA, *n* positive (negative, missing)	3 (2, 11)
Patients with available MRIs associated with baseline acute episode, *n*/total no. of patients	**15/16**
When MRI performed	
During an acute episode and while patient is receiving treatment, *n*	7
No acute lesions on MRI, *n* (%)	2 (28.6)
During an acute episode and patient is NOT receiving treatment, *n*	3
No acute lesions on MRI, *n* (%)	1 (33.3)
During quiescent period, *n*	5
No acute lesions on MRI, *n* (%)	0 (0.0)
Regional changes	
1 Optic nerve, *n* (% of no. of MRIs available)	5 (33.3)
2 Brain, *n* (% of no. of MRIs available)	3 (20.0)
3 Spinal cord, *n* (% of no. of MRIs available)	1 (6.7)
4 0 changes, *n* (% of no. of MRIs available)	3 (20.0)
1 + 2, *n* (% of no. of MRIs available)	3 (20.0)
1. Optic nerve involvement, *n*/total MRIs available	**8/15**
Unilateral, *n* (% of total no. of MRIs with optic nerve involvement)	6 (75.0)
Bilateral, *n* (% of total no. of MRIs with optic nerve involvement)	2 (25.0)
No. of MRIs presenting acute lesions in the following locations:	
Intraorbital, *no. of MRIs*	3
Prechiasm, *no. of MRIs*	5
Chiasm, *no. of MRIs*	2

Optic tracts, *no. of MRIs*	1
2. Brain involvement, *n*/total MRIs available	**6/15**
Single acute lesion, *n* (% of total no. of MRIs with brain involvement)	1 (16.7)
Multiple acute lesions, *n* (% of total no. MRIs with brain involvement)	5 (83.3)
No. of MRIs presenting supratentorial lesions	
Deep WM, *no. of MRIs*	3
Juxtacortical WM, *no. of MRIs*	3
Periventricular WM, *no. of MRIs*	2
Juxtaventricular WM, *no. of MRIs*	3
No. of MRIs presenting infratentorial lesions	
Pons, *no. of MRIs*	2
Pontine-mesencephalic transition, *no. of MRIs*	1
Mesencephalon, *no. of MRIs*	1
Cerebellum, *no. of MRIs*	1
Medulla oblongata, *no. of MRIs*	1
MRIs presenting chronic lesions[e]	**5**
3. Spinal cord involvement, *n*/total MRIs available	**1/15**
Contrast enhancement pattern present	Yes
Presentation of acute lesions	LETM
Most recent MRI (16 total patients)	
No later MRIs, *n*	6
Regression of previous lesions, *n*	3
New lesions present, *n*	2
Regression of previous lesions + new lesions detected, *n*	2
No lesions present, *n*	2
MRI comparable to MRI associated with baseline acute episode, *n*	1
Most recent OCT results	
Available OCTs	**14/16**

No history of ON, *n*/total OCTs available	**1/14**
Average RNFL thickness, RE, LE, µm	82, 79
RNFL symmetry, %	92
Average GCIPL thickness, RE, LE, µm	81, 82
GCIPL min. thickness, RE, LE, µm	81, 82
History of unilateral ON, *n*/total OCTs available	**6/14**
Concerning affected eye	
Average RNFL thickness, median (mean; min-max), µm	73 (74; 46-100)
RNFL symmetry, median (mean; min-max), %	83.5 (79.7; 61-93)
Average GCIPL thickness, median (mean; min-max), µm	67.5 (66.8; 53-80)
GCIPL min. thickness, median (mean; min-max), µm	65 (63.5; 47-78)
History of bilateral ON, *n*/total OCTs available	**7/14**
Concerning worst affected eye[f]	
Average RNFL thickness, median (mean; min-max), µm	72 (70.29; 52-89)
RNFL symmetry, median (mean; min-max), %	84 (71.80; 3-95)
Average GCIPL thickness, median (mean; min-max), µm	67.5 (68.50; 53-83)
GCIPL min. thickness, median (mean; min-max), µm	65 (62.67; 44-83)

[a] This section refers to the 11 patients that have a relapsing disease course and details the most common reason each patient suffered a relapse.

[b] Due to intraorbital inflammation, patient presented with involvement of elevator palpebrae superioris and right superior rectus.

[c] Results came back negative for all patients who underwent testing for anti-double stranded deoxyribonucleic acid (DNA) antibodies, extractable nuclear antibodies, anti-cytoplasmic and anti-perinuclear antineutrophil cytoplasmic antibodies, lupus anticoagulant antibodies, thyroid antibodies, antineuronal antibodies, serum anti-AQP4 IgG.

[d] 6 OCBs were common to CSF and serum - compatible with systemic inflammation.

[e] Chronic lesions seen on MRI: cerebral atrophy, neocortical gliosis, ventriculomegaly, corpus callosum atrophy, microcirculatory lesions.

[f] Eye considered to be worst affected was based on average RNFL and GCIPL thickness.

n, number of patients; EDSS, Expanded Disability Status Scale; σ, standard deviation; min., minimum; max., maximum; ARR, annualised relapse rate (episodes per patient per year); no., number; VA, visual acuity; LogMAR, Logarithm of the Minimum Angle of Resolution; RAPD, relative afferent pupillary defect; ANA, antinuclear antibodies; Abs, antibodies; CSF, cerebrospinal fluid; mg/dL, milligrams per decilitre; RBC, red blood cell; WBC, white blood cells; OCBs, oligoclonal bands; EBNA, Epstein-Barr nuclear antigen; MRI, magnetic resonance imaging; WM, white matter; LETM, longitudinally extensive transverse myelitis; alt., alterations; OCT, optical coherence tomography; ON, optic neuritis; RNFL, retinal nerve fibre layer; GCIPL, ganglion cell-inner plexiform layer; RE, right eye; LE, left eye; µm, micrometre.

3.2. Treatment regimens

Acute immunosuppressive treatment data is summarised in table 4, found in appendix I. The immunosuppressive treatment used in over 50% of acute episodes was in all patients was megadose methylprednisolone.

Concerning the baseline acute episode, megadose methylprednisolone monotherapy was used in nine (56.3%) patients and four (25%) patients received more than one drug to control the acute event. One of the patients receiving megadose methylprednisolone monotherapy did not have a complete response and there were no records for treatment response in one of the nine patients in this subgroup. Prednisolone taper was used in three patients.

At the baseline acute episode, immunosuppressive multitherapy was utilised in patients whose symptoms and/or physical exam findings did not markedly ameliorate after five to seven days of megadose methylprednisolone.

Table 4 also broadly summarises how the acute immunosuppressive regimen changed from our cohort's baseline to their most recent acute episode – changes which were only applicable to eight patients since the other eight patients' baseline acute episodes were also their most recent. Referring to the last section of table 4, we report that five of our eight patients' treatment regimens changed. The acute treatment regimen was stepped up in three patients. All three of these patients completely recovering from their most recent acute episode. The reasons for stepping up the treatment regimen in these patients was the following: 1) after initially only symptomatic treatment, one patient required better control of their acute episode and was given megadose methylprednisolone over seven days and intravenous immunoglobulin (IVIg) over five days. 2) A prednisolone taper (duration unspecified) was introduced after three days of megadose methylprednisolone in one patient since they suffer relapses whenever their corticosteroid dose falls below 10mg/day. 3) The third patient received a short, three-day course of megadose methylprednisolone to expedite recovery instead of e prednisolone taper that was given at the baseline acute episode.

Acute treatment was stepped down in two patients: 1) megadose methylprednisolone monotherapy was sufficient in controlling the episode of one patient who had previously received plasma exchange (PLEX) with megadose methylprednisolone. 2) The second patient received no acute immunosuppressive treatment and was only submitted to further investigation.

Current long-term immunosuppressive treatment in our patient cohort is outlined in table 5. All patients are considered to have achieved disease control with their current treatment regimen. Eight (50%) patients are receiving monotherapy; combination therapy is currently being implemented in four (25%) patients and four (25%) are in active disease vigilance. Mycophenolate mofetil for long-term disease control is being used in four out of eight monotherapy patients. Two of the three patients receiving corticosteroids as part of their combination therapy are corticosteroid dependent and the third is undergoing a taper.

In terms of the two patients with prior MS diagnoses: the patient diagnosed 25 years ago has relied on 1g monthly megadose methylprednisolone for the past six years due to poor response to base immunosuppressive therapy. This patient had previously received interferon beta-1a and glatiramer acetate with very poor response, maintaining continued disease progression, and is currently receiving tocilizumab in monotherapy and responding well.

Furthermore, one of the patients with a previous diagnosis of MS in a context of recurrent acute episodes of LETM ceased disease activity after add-on of interferon beta-1a to their azathioprine monotherapy regimen, 15 years before anti-MOG IgG1 testing.

Table 5. MOGAD current long-term immunosuppressive treatment.

Monotherapy, *n* (%)			**8 (50.0)**
	***n* (%)**	**Complete response, *n* (%)**	**Comments**
MMF	4 (50.0)	4 (100.0)	2 patients have monophasic course.
AZT	2 (25.0)	2 (100.0)	0
TOZ	1 (12.5)	1 (100.0)	0
IVIg	1 (12.5)	1 (100.0)	Paraneoplastic MOGAD; patient receiving Osimertinib 40 mg.
Dual therapy, *n* (%)			**3 (18.8)**
TOZ + corticosteroid	2 (66.7)	2 (100.0)	One patient receiving MPD 1g monthly; the other patient receiving PD 15mg id. Both patients are corticosteroid dependent.
AZT + IFN beta-1a	1 (33.3)	1 (100.0)	AZT monotherapy unable to control disease; control achieved after adding IFN beta-1a.
Triple therapy, *n* (%)			**1 (6.3)**

TOZ + MTX + Corticosteroid	1 (100.0)	1 (100.0)	PD is gradually being tapered; MTX initiated due to incomplete response to TOZ.
Maintains active vigilance only, *n* (%)			**4 (25.0)**
			1 patient has disease completely stabilised. 3 patients with monophasic course and disease stabilised.

n, number of patients; MMF, mycophenolate mofetil; AZT, azathioprine; TOZ, tocilizumab; MPD, methylprednisolone; IVIg, intravenous immunoglobulin; IFN beta-1a, interferon beta-1a; MTX, methotrexate; PD, prednisolone; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; g, gram; mg, milligram; id, once a day.

Table 6 displays the long-term treatment previously trialled in our patient cohort, along with details concerning the total number of drugs trialled, reason(s) for suspension and current long-term immunosuppressive treatment. A summary of the patient's disease profile was also provided for context. The most typical reasons for past treatment failure or changes in treatment regimen are 1) switch to steroid-sparing treatment or 2) treatment inefficacy – patient continued to suffer relapses or demonstrated maintained clinical deterioration or decline on imaging tests. Treatment failure was most associated with azathioprine, occurring in four patients, followed by rituximab treatment failure which occurred in three patients.

Table 6. MOGAD prior long-term immunosuppressive treatment.

n, number of patients; info., information; anti-MOG IgG; anti-myelin oligodendrocyte glycoprotein immunoglobulin G; MMF, mycophenolate mofetil; AZT, azathioprine; RTX, rituximab; TOZ, tocilizumab; PLEX, plasma exchange; IVIg, intravenous immunoglobulin; IFN beta-1a, interferon beta-1a; MTX, methotrexate; PD, prednisolone; EDSS, Expanded Disability Status Scale; Sx, syndrome; TB, tuberculosis; MS, multiple sclerosis; RNFL, retinal nerve fibre layer; GCL, ganglion cell layer.

1 drug previously trialled, *n* (%)				**8 (50.0)**
		Reason for suspension	**Current treatment**	**Patient info.**
Corticosteroid, *n* (%)	4 (50.0)	1) Initiated steroid-sparing treatment. 2) Initiated steroid-sparing treatment. 3) Achieved disease control. 4) Achieved disease control.	1) MMF 2) AZT 3) Active vigilance. 4) Active vigilance.	1) Maintained high anti-MOG IgG titres. Predominant optic + brainstem involvement. EDSS 1 -> 0. 2) Predominant brainstem involvement. EDSS 3.5 -> 1. 3) EDSS 2 -> 1. 4) Predominant optic involvement. EDSS 3 -> 1.
RTX, *n* (%)	2 (25.0)	1) Treatment inefficacy. 2) Treatment inefficacy.	1) MMF 2) TOZ	1) Predominant optic involvement. EDSS 4 -> 4. 2) Predominant optic and cerebral involvement. EDSS 3.5 -> 1.
MMF, *n* (%)	1 (12.5)	Treatment inefficacy.	TOZ + Corticosteroid	Patient maintained annual loss of 10micra of RNFL and 4micra of GCL even though they did not have acute episode. Predominant optic involvement. EDSS 3.5 -> 1.5.
AZT, *n* (%)	1 (12.5)	Treatment inefficacy.	AZT + IFN beta-1a	Patient with previous diagnosis of MS and recurrent myelitis and optic involvement. EDSS 2.5 -> 3.5.
2 drugs previously trialled, *n* (%)				**3 (18.8)**
AZT; corticosteroid, *n* (%)	1 (33.3)	AZT side effects; initiated steroid-sparing treatment.	MMF	Predominant optic involvement. EDSS 3 -> 1.
PLEX; corticosteroid, *n* (%)	1 (33.3)	TB patient who initiated steroid-sparing treatment.	AZT	Predominant optic involvement. EDSS 3 -> 1.
AZT; RTX, *n* (%)	1 (33.3)	AZT treatment inefficacy; RTX patient had anaphylactic reaction.	TOZ + MTX + Corticosteroid	Predominant optic involvement and patient is corticosteroid dependent. EDSS 3 -> 1.
≥3 drugs previously trialled, *n* (%)				**2 (12.5)**
IFN beta-1a; glatiramer acetate AZT; RTX; MMF, *n* (%)	1 (50.0)	Treatment inefficacy.	TOZ + monthly 1g corticosteroid	Patient with previous diagnosis of MS. EDSS 4 -> 4.5.
Corticosteroid; MTX; AZT, *n* (%)	1 (50.0)	Corticosteroid side-effects; treatment inefficacy; treatment inefficacy.	MMF	Predominant optic involvement. Maintains EDSS 3.
0 prior long-term treatment				**3 (18.8)**
		-	1) Maintain disease vigilance. 2) Maintain disease vigilance. 3) Long-term treatment (IVIg) initiated after first relapse.	1) Apparently monophasic course (ptosis). EDSS 3 -> 0. 2) Apparently monophasic course (optic). EDSS 4 -> 1. 3) Paraneoplastic MOGAD. EDSS 3 -> 2.

3.3. Disease prognosis

Table 7 (MOGAD prognosis based on initial anti-MOG IgG1 titre) and table 8 (MOGAD prognosis based on total number of acute episodes) are available in appendix II and III, respectively. An initial low anti-MOG IgG1 titre (≤1:10) or a low total number of relapses (≤3) did not demonstrate any correlation with disease prognosis in our cohort of MOGAD patients.

Based on tables 7 and 8, we further investigated 1) the correlation between age at onset and current EDSS, 2) age at onset and total number of acute episodes, and 3) EDSS at inaugural episode and total number of acute episodes. There was a trend to a higher number of relapses in younger patients and the number of days between symptom onset at the baseline episode and beginning of immunotherapy was correlated with higher patient recovery status. The results of this analysis are presented in table 9, found in appendix IV.

4. DISCUSSION

In our study, the difference in incidence between the genders was marginal and the incidence of concomitant autoimmune disease was uncommon, corroborating findings in other studies of MOGAD patients. (14–16) Over half of our cohort was given an initial diagnosis within the optic nerve disorders spectrum, specifically ON, NMOSD or MS; diagnosis continued to prove challenging when presentation was atypical or similar to other demyelinating diseases, shown by the four-year difference between mean age at onset and mean age at diagnosis. Studies (11) frequently document the occurrence of an infectious prodrome and/or vaccination history prior to an acute episode. According to our data, two patient records made reference to a recent history of respiratory and gastrointestinal infection prior to their inaugural episode. However, it is not possible to concretely exclude infectious or vaccination events in the remaining 14 patients since this information was not specifically negated in their medical records.

ON was the most common acute phenotype along disease course, with slight predominance of unilateral optic nerve involvement at the baseline acute episode. MOGAD habitually does not share the same “typical” ON features of MS; instead, “atypical” ON manifestations in a patient, including bilateral involvement, extensive optic nerve lesions, severe VA loss and marked optic nerve head oedema were present in our cohort, as described in literature. (17) VA LogMAR values were highly variable and dyschromatopsia was typically severe in our cohort. OCT data recorded that only half of patients had a history of bilateral ON (whether bilateral optical nerve involvement was simultaneous or sequential). These findings are not concordant with results from studies such as Ramanathan S et al (9) where there is a stronger pattern of bilateral ON in MOGAD patients. Acute manifestation of cerebral demyelinating lesions was by far the rarest occurrence, arising in only one patient who has the longest disease course in the cohort. Typically, patients only had one isolated (relapsing) phenotype over their disease course, however this was not the case in a quarter of our cohort where more than one phenotype arose after onset. A study conducted by Cross et al, (18) however, reported that 26/34 patients experienced different phenotypes to that at the inaugural episode. In our study, under a quarter of patients displayed a simultaneous combination of phenotypes with *optical* + *spinal cord* or *optical* + *brainstem* involvement most typically occurring

In terms of confounding presentations, we report two patients with previous presumptive diagnoses of MS, before MOGAD as an entity was described, both with recurrent myelitis associated with ON. Correct diagnosis in these cases is made more difficult since there were no involvement of the conus medullaris in any of their MRIs – a feature which is more common in MOGAD patients. (20) In these unclear cases, it is highly important to submit patients to

autoantibody testing in order to correctly identify the underlying disease. None of our patients presented symptomatology most commonly found in NMOSD: singultus, intractable cough or nausea, vomiting or narcolepsy, among others. (19)

EBNA testing was inconsistent in our patient cohort, but of the patients who underwent testing, positivity to prior Epstein Barr Virus infection was reported in 60% of cases, suggesting that infection may be a possible MOGAD trigger, as reported by other studies. (21) Anti-MOG IgG1 autoantibodies are produced peripherally, and our study concordantly does not report any patients with CSF-restricted OCBs. Where medical records contained a concrete titre value, patients with concomitant immunologically mediated pathologies (autoimmune, infectious or neoplastic) almost always presented high initial and/or recent anti-MOG IgG1 titre values ($\geq$1:32). However, this finding was not exclusive to this patient subset and a larger cohort would permit a more careful analysis. One patient had an initially negative titre, highlighting the importance of the carefully timing autoantibody testing with immunosuppressive treatment; the testing method is also important to consider, with cell-based assays being the gold standard; and finally, medical health professionals should consider repeating autoantibody tests in suspicious or unclear cases.

The cohort's MRI results were heterogenous, with MRIs occasionally not evidencing lesions when a patient has positive clinical findings or evidencing lesions in asymptomatic patients. This second finding highlights the importance of MRI in monitoring subclinical MOGAD activity. Of the MRIs demonstrating lesions, optic nerve involvement was the most common manifestation with the majority presenting unilateral lesions in the anterior nerve section (intraorbital and prechiasmatic) which is a common MOGAD marker found in other studies. (18,22) The most recently available OCT data was collected in order to evaluate the repercussions on the optic nerve. Performing regular OCTs in MOGAD patients is particularly beneficial since this imaging technique more accurately evidences optic nerve damage and permits closer monitoring and detection of subclinical demyelinating events. (23) Table 2 summarises the OCT results of our patients and we note a reduction of RNFL and GCIPL in patients with a history of ON when compared to the OCT findings of the patient with no ON history. Neuro-ophthalmological deterioration occurs with ON relapses (23) and we also have cases of subclinical deterioration of the retina.

MOGAD, in concordance with previous studies, (24) is highly responsive to corticosteroid therapy and our cohort contains patients dependent on chronic corticotherapy. In order to avoid the long-term side-effects of corticotherapy, steroid-sparing treatment should be optimised whenever possible. A small proportion of our patients received a prednisolone taper to control the baseline acute episode, often as part of a multi-immunosuppressive regimen, with variable

response and duration. Possible challenges in controlling more serious acute presentations and/or the divergence in patient phenotypes may explain the less-than desirable response in the patient groups who received multi-immunotherapy regimens at their acute baseline episodes. For long-term immunosuppression, normally DMTs approved for MS are not recommended in neuromyelitis optica (NMO) patients due to the fact that there is either no patient response or they may incite disease exacerbation. (25) This was demonstrated in the case of a patient with a prior MS diagnosis who received interferon beta-1a and glatiramer acetate with very poor response. Contrastingly, we also have one particular atypical case of a patient with a prior MS diagnosis whose disease course improved after adding interferon beta-1a to their treatment regimen.

Active vigilance is being implemented in a quarter of our patients. This conservative attitude is attributed to the fact that the majority of these patients have so far demonstrated a monophasic disease course and the rest have repeatedly exhibited disease stabilisation in their follow-up consultations.

Overall, the cohort's outcome was favourable with mean EDSS falling over disease course. According to our findings, the EDSS at the inaugural acute episode was worse than at the episode at diagnosis, suggesting either a possible gradual improvement of disease impact on patients or success in controlling disease progression. Interestingly, our cohort's anti-MOG IgG1 titre generally rose over the disease. We suggest continued follow-up of patients who presented clinically ambiguous lesions on their most recent MRI in order to monitor possible evolution and eventually, adjust treatment. One factor we identified that could eventually have an impact on patient recovery after a demyelinating event was treatment delay after symptom onset; data suggests that there was a tendency for complete recover the less time it took for a patient to initiate immunomodulating treatment. We also report a higher mean of acute episodes in younger patients (19-24 years).

Limitations of our study include: 1) the retrospective design of this study, 2) this study did not include the paediatric population. However, children with MOGAD tend to present a different disease course, clinical characteristics and radiological findings (26) and we intended to perform an adult population study. 3) Another limitation was the small sample size of 16 participants which limited our ability to draw statistically significant conclusions. According to a national study, Portugal has a total of 67 recorded seropositive MOGAD patients, (14) including paediatric cases. 4) Anti-MOG IgG1 detection in CHUC was rolled out in November 2018, therefore this had implications on the interpretation of MOGAD's natural disease timelines, including mean age at diagnosis, which we tried to mitigate by calculating the total ARR and the post diagnosis ARR. 5) In addition, in order to include as many seropositive MOGAD

patients as possible, many of our patients had a follow-up time of ≤8 years which meant that a rich and detailed description of MOGAD's full disease course was not always possible and patients that appeared to be monophasic may, in fact, later present a relapsing course. 6) Furthermore, during data collection, we detected inconsistent and infrequent use of contrast in MRI procedures and therefore we generally excluded data concerning contrast enhancement in order to maintain data homogeneity.

5. CONCLUSION

Our study identified optic neuritis as the principal presentation in our cohort with bilateral optical involvement in half of our cohort and favourable outcomes with EDSS reducing from an initial 3.0 to a current 1.66. OCT and follow-up MRIs have proven to be useful tools in monitoring disease progression. Our study did not demonstrate any statistically significant correlation between prognosis and initial anti-MOG IgG1 titre or total number of acute episodes. However, we report a trend suggesting younger patients have a higher number of relapses and we also observed a higher patient recovery in patients with reduced delay between symptom onset and beginning of immunotherapy. Based on the anti-MOG IgG1 titre results, it is important for the medical health professional to maintain high levels of suspicion in ambiguous cases and insist if initial autoantibody panel test results return negative.

Further investigation into disease prognostic markers will permit a better comprehension of disease evolution and appropriate patient follow-up within MOGAD's wide spectrum. In addition, we recommend further clinical trials and investigation into immunotherapy to assess patient eligibility for active vigilance regimens and in cases where immunotherapy is required, how to select effective immunosuppressive drugs to control disease.

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Segredos desta cidade
Levo comigo p'rá vida.

– Balada da Despedida

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9. APPENDIX

APPENDIX I. MOGAD acute immunosuppressive treatment table.

Table 4. MOGAD acute immunosuppressive treatment.

Most commonly used acute immunosuppressive treatment[a]	
Megadose methylprednisolone, *n* (%)	16 (100.0)
Acute treatment used at baseline acute episode, *n* (%)	**16 (100.0)**
MGD, *n* (%)	9 (56.3)
Complete response, *n*/no. of available response records	7/8
Missing response data, *n* (%)	1
MGD + PLEX, *n* (%)	2 (12.5)
Complete response, *n* (%)	0 (0.0)
MGD + PLEX + PD taper, *n* (%)	2 (12.5)
Complete response, *n* (%)	0 (0.0)
PD taper, *n* (%)	1 (6.3)
Complete response, *n* (%)	1 (100.0)
Symptomatic treatment, *n* (%)	2 (12.5)
Complete response, *n* (%)	-
Acute treatment used at most recent acute episode, *n* (%)	**8 (50.0)[b]**
Maintained same acute treatment as baseline episode, *n* (%)	3 (37.5)
Treatment stepped up, *n* (%)	3 (37.5)
Treatment stepped down, *n* (%)	2 (25.0)

[a] Acute immunosuppressive treatment used in >50% of acute episodes in a patient.

[b] 8 patients were excluded from this section because their most recent episode was their baseline acute episode.

n, number of patients; no., number; MGD, megadose methylprednisolone (1g/day); PD taper, prednisolone taper; PLEX, plasma exchange.

APPENDIX II. MOGAD prognosis based on initial anti-MOG IgG1 titre table.

Table 7. MOGAD prognosis based on initial anti-MOG IgG1 titre.

	Initial anti-MOG IgG1 titre ≤1:10	**Initial anti-MOG IgG1 titre >1:10**	***p***
Total number of patients: 16	10	6	
Age at inaugural episode, mean (median; min-max), years	39.90 (41.50; 21-62)	42.20 (41; 25-60)	0.875
Time between inaugural episode and diagnosis, mean (median; min-max), years	2.61 (1.49; 0.11-7.81)	6.30 (0.03; 0.01-22.64)	0.313
Disease course			
Monophasic, *n* (%)	2 (20.0)	3 (50.0)	0.242
Relapsing, *n* (%)	8 (80.0)	3 (50.0)	
Total number of acute episodes, median (mean; min-max)	3.5 (4; 1-8)	2 (6; 1-25)	0.562
ARR			
Since inaugural episode, mean (median; min-max)	0.82 (0.55; 0.20-1.80)	1.58 (0.81; 0.20-6.00)	0.792
After MOGAD diagnosis, mean (median; min-max)	0.69 (0.49; 0.30-2.00)	1.96 (1.01; 0.10-6.40)	0.313
EDSS at inaugural episode			
≤2.5, *n* (%)	2 (20.0)	0 (0.0)	0.375
3 - 4.5, *n* (%)	8 (80.0)	6 (100.0)	
EDSS at last observation			
≤2.5, *n* (%)	8 (80.0)	4 (66.7)	0.489
3 - 4.5, *n* (%)	2 (20.0)	2 (33.3)	
Presentation of all acute episodes over disease course			
ON, *n* (%)	6 (60.0)	4 (66.7)	1.000
Brainstem involvement , *n* (%)	1 (10.0)	0 (0.0)	
Spinal involvement, *n* (%)	0 (0.0)	0 (0.0)	
Cerebral involvement, *n* (%)	0 (0.0)	0 (0.0)	
>1 presentation, *n* (%)	3 (30.0)	2 (33.3)	
Most recent observation			
VA, mean (median; min-max), LogMAR	0.69 (0.05; 0-3)	0.34 (0.10; 0.00-1.30)	0.876

Visual field defects, *n* (%)	1 (10.0)	1 (16.7)	0.685
RAPD, *n* (%)	4 (40.0)	1 (16.7)	
Motor alt., *n* (%)	1 (10.0)	2 (33.3)	
Brainstem alt., *n* (%)	1 (10.0)	2 (33.3)	
Current long-term immunosuppressive treatment			
Monotherapy, *n* (%)	6 (60.0)	2 (33.3)	0.601
Dual therapy, *n* (%)	1 (10.0)	2 (33.3)	
Triple therapy, *n* (%)	1 (10.0)	0 (0.0)	
0, only active vigilance, *n* (%)	2 (20.0)	2 (33.3)	
Most recent anti-MOG IgG1 titre >1:10, *n* (% of available results)	6 (66.7)	3 (60)	1.000
Abnormalities in MRI of baseline acute episode			
Brain, *n*	4	2	0.528
Optic nerve, *n*	5	2	
Spine, *n*	0	1	
Most recent MRI presents new lesions and/or maintains previous lesions, *n* (% of available MRIs)	3 (50.0)	1 (25.0)	0.528
Most recent OCT			
History of unilateral ON, *n*/total OCTs available	**5/9**	**1/5**	
Concerning affected eye			
Average RNFL thickness, mean (median; min-max), µm	76.2 (75; 46-136)	63	
RNFL symmetry, mean (median; min-max), %	78 (81; 61-93)	90	
Average GCIPL thickness, mean (median; min-max), µm	69.6 (74; 53-80)	53	
GCIPL min. thickness, mean (median; min-max), µm	66.2 (72; 47-78)	50	
History of bilateral ON, *n*/total OCTs available	**3/9**	**4/5**	
Concerning worst affected eye			
Average RNFL thickness, mean (median; min-max), µm	74 (72; 61-89)	67.5 (69.5; 52-79)	0.629
RNFL symmetry, mean (median; min-max), %	57 (83; 3-85)	87 (86; 79-95)	0.400
Average GCIPL thickness, mean (median; min-max), µm	64 (66.7; 53-83)	70.3 (71; 64-76)	0.700
GCIPL min. thickness, mean (median; min-max), µm	58.3 (48; 44-83)	67 (71; 59-71)	0.700

Anti-MOG IgG1, anti-myelin oligodendrocyte glycoprotein immunoglobulin G1; *n*, number of patients; min., minimum; max., maximum; ARR, annualised relapse

rate; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; EDSS, Expanded Disability Status Scale; ON, optic neuritis; VA, visual acuity; LogMAR, Logarithm of the Minimum Angle of Resolution; RAPD, relative afferent pupillary defect; alt., alterations; MRI, magnetic resonance imaging; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer; GCIPL, ganglion cell-inner plexiform layer; CDR, cup-to-disc ratio; µm, micrometre; mm^2, square millimetre; mm^3, cubic millimetre.

APPENDIX III. MOGAD prognosis based on total number of acute episodes table.

Table 8. MOGAD prognosis based on total number of acute episodes.

	Total number of acute episodes ≤3	**Total number of acute episodes >3**	***p***
Total number of patients: 16	9	7	
Age at inaugural episode, mean (median; min-max), years	43.76 (44; 25-62)	37 (39; 21-53)	0.351
EDSS at inaugural episode			
≤2.5, *n* (%)	1 (11.1)	1 (14.3)	1.000
3 - 4.5, *n* (%)	8 (88.9)	6 (85.7)	
EDSS at last observation			
≤2.5, *n* (%)	8 (88.9)	4 (57.1)	0.262
3 - 4.5, *n* (%)	1 (11.1)	3 (42.9)	
Presentation of all acute episodes over disease course			
ON, *n* (%)	7 (77.8)	3 (42.9)	0.106
Brainstem involvement, *n* (%)	1 (11.1)	0 (0.0)	
Spinal involvement, *n* (%)	0 (0.0)	0 (0.0)	
Cerebral involvement, *n* (%)	0 (0.0)	0 (0.0)	
>1 presentation, *n* (%)	1 (11.1)	4 (57.1)	
Most recent observation			
VA, mean (median; min-max), LogMAR	0.35 (0.05; 0.00-2.30)	0.75 (0.10; 0-30)	0.852
Visual field defects, *n* (%)	1 (11.1)	1 (14.3)	1.000
RAPD, *n* (%)	2 (22.2)	3 (42.9)	
Motor alt., *n* (%)	1 (11.1)	2 (28.6)	
Brainstem alt., *n* (%)	2 (22.2)	1 (14.3)	
Current long-term immunosuppressive treatment			
Monotherapy, *n* (%)	6 (66.7)	2 (28.6)	0.076
Dual therapy, *n* (%)	0 (0.0)	3 (42.9)	
Triple therapy, *n* (%)	0 (0.0)	1 (14.3)	
0, only active vigilance, *n* (%)	3 (33.3)	1 (14.3)	

Most recent anti-MOG IgG1 titre >1:10, *n* (% of available results)	5 (55.6)	4 (80.0)	0.580
Most recent MRI presents new lesions and/or maintains previous lesions, *n* (% of available MRIs)	2 (33.3)	3 (75.0)	1.000
Most recent OCT			
History of unilateral ON, *n*/total OCTs available	**2/9**	**4/5**	
Concerning affected eye			
Average RNFL thickness, mean (median; min-max), µm	76	73 (73; 46-100)	1.000
RNFL symmetry, mean (median; min-max), %	88	76 (74; 61-93)	0.533
Average GCIPL thickness, mean (median; min-max), µm	66.5	67 (67.5; 53-80)	1.000
GCIPL min. thickness, mean (median; min-max), µm	63	63.8 (65; 47-78)	1.000
History of bilateral ON, *n*/total OCTs available	**6/9**	**1/5**	
Concerning worst affected eye			
Average RNFL thickness, mean (median; min-max), µm	73.3 (72; 61-89)	52	
RNFL symmetry, mean (median; min-max), %	72 (84; 3-95)	*	
Average GCIPL thickness, mean (median; min-max), µm	68.5 (67.5; 53-83)	*	
GCIPL min. thickness, mean (median; min-max), µm	62.7 (65; 44-83)	*	

* Missing data.

Min., minimum; max., maximum; EDSS, Expanded Disability Status Scale; *n*, number of patients; ON, optic neuritis; VA, visual acuity; LogMAR, Logarithm of the Minimum Angle of Resolution; RAPD, relative afferent pupillary defect; alt., alterations; anti-MOG IgG1, anti-myelin oligodendrocyte glycoprotein immunoglobulin G1; MRI, magnetic resonance imaging; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer; GCIPL, ganglion cell-inner plexiform layer; CDR, cup-to-disc ratio; µm, micrometre; mm^2, square millimetre; mm^3, cubic millimetre.

APPENDIX IV. Table of MOGAD prognosis markers.

Table 9. MOGAD prognosis markers.

Age at onset, years		**Current EDSS, *mean* (min-max)**	**Total number of acute episodes, *mean* (min-max)**
19-24, *n* (%)	2	1.25 (1.0-1.5)	6.5 (5-8)
25-44, *n* (%)	8	2.25 (0.0-4.5)	5.5 (1-25)
45-65, *n* (%)	6	1.00 (0.0-2.0)	3.2 (1-8)
66-80, *n* (%)	0	-	-
EDSS at inaugural episode		**Total number of acute episodes, *mean* (min-max)**	
0.0 to 2.5, *n* (%)	2		3 (2-4)
3.0 to 3.5, *n* (%)	10		3.8 (1-8)
4.0 to 4.5, *n* (%)	2		1 (1-1)
≥5.0, *n* (%)	0		-
Missing data, *n* (%)	2		-
Time between symptom onset and immunotherapy, days		**Recovery status, *complete recovery* %**	
≤1, *n* (%)	3[a]		100.0
2-5, *n* (%)	6		66.6
>5, *n* (%)	3[b]		0.0
Missing data, *n* (%)	4		-

[a] One patient only received symptomatic treatment at acute episode and was not included in the calculation of the proportion of patients with complete recovery.

[b] One patient only received symptomatic treatment at acute episode and was not included in the calculation of the proportion of patients with complete recovery.

n, number of patients; EDSS, Expanded Disability Status Scale; min., minimum; max., maximum.