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BRAIN VOLUMES AND COGNITION IN MOG ANTIBODY-ASSOCIATED DISEASE: AN ITALIAN MULTICENTER LONGITUDINAL STUDY

S.S.D. MED/26

Coordinator: Prof. Michela Rimondini

Tutor: Prof. Alberto Gajofatto

Doctoral Student: Dr Riccardo Orlandi

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ABSTRACT

Background. Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a recently recognized demyelinating disorder whose clinical features partly overlap with Multiple Sclerosis (MS). MRI is, to date, one of the best tools to differentiate these diseases; however, little is known about brain atrophy, disease progression on brain MRI and neuropsychological (NPS) profile of MOGAD patients compared to MS.

Objectives. This multicenter longitudinal study compares global, white matter, gray matter and regional brain MRI volumes and T2 lesion volume between MOGAD, relapsing-remitting MS (RRMS) patients and a healthy control (HC) group with brain MRI scans available from an online repository.

Methods. 16 adult MOGAD patients (9 F) with a clinical follow-up ≥6 months have been selected from an ongoing multicenter observational study which started the recruitment on 31/01/2017. 44 RRMS patients (26 F) fulfilling 2017 McDonald Criteria, homogenous for age and sex to the MOGAD cases, and a clinical follow-up ≥6 months have been recruited in Verona MS center through the consultation of an electronic database. For both MOGAD and MS patients, clinical and NPS assessments (BICAMS battery), as well as brain MRI scan, are performed at T0 and after 18±6 months. T1-3D and FLAIR-3D scans are used for volumetric analysis, with the same MRI protocol and scanner at both timepoints for each patient. Annualized percentage brain volume change (PBVC/y) between the two MRI timepoints, baseline global brain, white matter (WM), grey matter (GM) and regional brain volumes are compared between groups using SIENA, SIENAX and VolBrain softwares. T2 lesion volume is assessed using ITK-snap. A group of 14 age- and sex-matched HC has been also added as comparator.

Results. MOGAD patients show no lesions on brain MRI in 50% of cases, and they have significantly less cortical, periventricular, juxtacortical, callosal and brainstem lesions compared with MS group. PBVC/y is lower in MOGAD than in RRMS ($p=0.014$), and lower in HC than in MS patients ($p=0.005$). Overall, MOGAD shows higher mean global brain ($p=0.012$) and WM volume ($p=0.024$), but lower median T2-lesion volume at timepoint 1 ($p<0.001$) compared to MS; T2-lesion volume increases over time in RRMS ($p<0.001$) but not in MOGAD cohort ($p=0.262$). NPS performances are comparable between MOGAD and MS patients, and only one MS and one MOGAD patient

fails one of the BICAMS tests. No significant correlations have been established between NPS tests scores and volumetric variables at T0.

Conclusions. Structural brain MRI features of MOGAD are characterized by higher global brain and WM volumes as well as less brain volume loss over time compared to RRMS. Lesion distribution has different topography in the two diseases. Moreover, MS shows an increase in T2 volume which is not detected in MOGAD, suggesting different underlining pathogenetic mechanisms.

SOMMARIO

Introduzione. La malattia associata ad anticorpi anti-glicoproteina oligodendrocitica mielinica (MOGAD) è una patologia demielinizzante recentemente riconosciuta, le cui caratteristiche cliniche si sovrappongono parzialmente alla Sclerosi Multipla (SM). Attualmente, la risonanza magnetica (RM) rappresenta uno dei migliori strumenti per differenziare queste malattie; tuttavia, sono scarse le evidenze circa l'atrofia cerebrale, la progressione della malattia evidenziata tramite RM e il profilo neuropsicologico (NPS) dei pazienti con MOGAD rispetto alla SM.

Obiettivi. Questo studio multicentrico longitudinale confronta i volumi cerebrale globale, della sostanza bianca, della sostanza grigia e i volumi regionali ottenuti tramite RM, e il volume delle lesioni T2 tra i pazienti MOGAD, i pazienti con sclerosi multipla recidivante-remittente (SMRR) e un gruppo di controlli sani (HC) con RM encefalo estratte da un repository online.

Metodi. Sono stati selezionati 16 pazienti adulti con MOGAD (9 F), con un follow-up clinico ≥6 mesi, da uno studio osservazionale multicentrico in corso che ha avviato l'arruolamento il 31/01/2017. 44 pazienti con SMRR (26 F), che soddisfano i criteri di McDonald 2017, omogenei per età e sesso rispetto ai casi di MOGAD, e con un follow-up clinico ≥6 mesi, sono stati reclutati presso il centro SM di Verona attraverso la consultazione di un database elettronico. Per entrambi i pazienti con MOGAD e SM, sono stati eseguiti valutazioni cliniche e NPS (batteria BICAMS), oltre a RM encefalo, a T0 e dopo 18±6 mesi. Sono state utilizzate sequenze T1-3D e FLAIR-3D per l'analisi volumetrica, con lo stesso protocollo MRI e lo stesso scanner a entrambi i timepoints per ciascun paziente. La variazione percentuale di volume cerebrale annualizzata (PBVC/y) tra i due timepoints di RM, il volume cerebrale normalizzato (NBV), della sostanza bianca (WM), della sostanza grigia (GM) e i volumi cerebrali regionali sono stati confrontati tra i gruppi utilizzando i software SIENA, SIENAX e VolBrain. Il volume delle lesioni T2 è stato valutato utilizzando ITK-snap. È stato aggiunto anche un gruppo di 14 HC abbinati per età e sesso come comparatore per le analisi eseguite con SIENA e SIENAX.

Risultati. I pazienti con MOGAD non presentano lesioni alla MRI cerebrale nel 50% dei casi, e mostrano significativamente meno lesioni corticali, periventricolari, juxtacorticali, del corpo calloso e tronco encefalico rispetto al gruppo SM. Il PBVC/y è inferiore in MOGAD rispetto a RRMS (p=0.014), e inferiore in HC rispetto ai pazienti SM

(p=0.005). Complessivamente, i casi MOGAD mostrano, rispetto agli SMRR, un maggiore NBV (p=0.012) e un volume maggiore della WM (p=0.024), ma un volume mediano inferiore delle lesioni T2 al timepoint 1 (p<0.001); il volume mediano delle lesioni T2 aumenta nel tempo nella RRMS (p<0.001) ma non nella coorte MOGAD (p=0.262). Le performance nei test neuropsicologici (NPS) sono comparabili tra i pazienti affetti da MOGAD e SM, con solo un paziente SM e uno MOGAD che non superano uno dei test BICAMS. Non sono state stabilite correlazioni significative tra i punteggi dei test NPS e le variabili volumetriche a T0.

Conclusioni: Le caratteristiche strutturali dell'RM encefalo della MOGAD sono definite da volumi cerebrali globali e di sostanza bianca superiori e da una minore perdita di volume cerebrale nel tempo rispetto alla SM-RR. La distribuzione delle lesioni ha una topografia diversa nelle due malattie. Inoltre, la SM mostra un aumento del volume T2 che non viene rilevato nella MOGAD, suggerendo meccanismi patogenetici sottostanti differenti.

INDEX

INTRODUCTION

1. INFLAMMATORY DEMYELINATING DISEASES OF THE CENTRAL NERVOUS SYSTEM

Inflammatory demyelinating diseases (IDD) are a broad spectrum of neurological disorders characterized by inflammation and neurodegeneration of the central nervous system (CNS). They represent the leading cause of nontraumatic neurological disability in young adults[1].

The pathologic hallmark of IDDs is demyelination, an immune-mediated damage of myelin sheath wrapping the CNS axons and of oligodendrocytes themselves; however, the pathogenetic mechanisms underlying demyelination differ among IDDs. From the neuroimaging perspective, this large group of disorders is characterized by similar lesions that need to be carefully differentiated according to their topography, extension, distribution and evolution over time.

IDDs can be divided into two groups: secondary demyelinating disorders, due to a known cause such as infections, malnutrition, intoxication, or deficiency diseases; and primary IDDs, in which immune-mediated demyelination is the core finding and pathological feature. The latter encompass a wide spectrum of conditions and phenotypes, that, in some cases, are associated with specific biomarkers. Multiple Sclerosis (MS) is the most common IDD of the CNS, affecting over 2.8 million people worldwide[2]. Some specific manifestations, such as Marburg disease, Schilder's disease and Baló's concentric sclerosis are considered MS-variants[3]. Neuromyelitis Optica Spectrum Disorder (NMOSD) is a much rarer condition, whose pathogenesis, in the majority of cases, is driven by the presence of serum Aquaporin-4 IgG (AQP4-IgG)[4]. More recently, a new disease entity, characterized by the presence of antibodies against Myelin Oligodendrocyte Glycoprotein (MOG), and whose clinical picture partly overlaps with seronegative NMOSD, has been added to the group of primary IDDs: MOG antibody-Associated Disease (MOGAD)[5].

2. MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY-ASSOCIATED DISEASE

MOG is a highly conservative protein which is exclusively expressed by oligodendrocytes in the CNS. Its biological role is still debated; however, its encephalitogenic potential has been widely demonstrated by several studies on experimental autoimmune encephalomyelitis (EAE) model[6]. Hence, antibodies against MOG (MOG-IgG) have been extensively investigated during the last decades in several IDDs. However, only in 2007 it was shown that laboratory assays expressing MOG in its tridimensional conformational form identified a subset of conformation-sensitive MOG-IgG in patients with acute disseminated encephalomyelitis (ADEM) or optic neuritis, but not in patients with MS[7]. The subsequent adoption of cell-based assays (CBAs) using human full-length MOG expressed on mammalian cells confirmed the detection of MOG-IgG in patients with non-MS IDDs, including 30–70% of patients with seronegative NMOSD[8,9].

2.3 EPIDEMIOLOGY

MOGAD is a rare condition, and studies investigating the worldwide burden of the disease are still scarce. Its prevalence is approximately 1.3-2.5 cases/100.000 and the annual incidence is estimated in 3.4-4.8 cases/million people[10,11] (Fig. 1).

According to the few evidence available, MOGAD seems relatively more prevalent across the Caucasian population compared to AQP4 IgG-positive NMOSD (NMOSD-AQP4)[11,12], although no obvious racial predominance has emerged from existing epidemiology studies.

No clear sex difference has emerged for MOGAD, compared to the higher prevalence in the female sex both for MS (female to male ratio 2-3:1)[13] and NMOSD-AQP4 (female to male ratio 9:1)[12].

Disease onset occurs at an earlier age compared to patients with NMOSD-AQP4. Combining data from studies that utilized CBAs in individuals with non MS-like IDDs who tested negative for serum AQP4-IgG, a clear correlation of MOG-IgG prevalence with age can be observed. The proportion of patients is higher in children (39%) compared to mixed adult-child cohorts (29%) or those of adults alone (23%). Hence,

MOGAD incidence can be split in two peaks, the first one occurring at pediatric age (onset between 9 and 12 years), while the second one is set in adulthood (approximately between 28 and 36 years of age)[14].

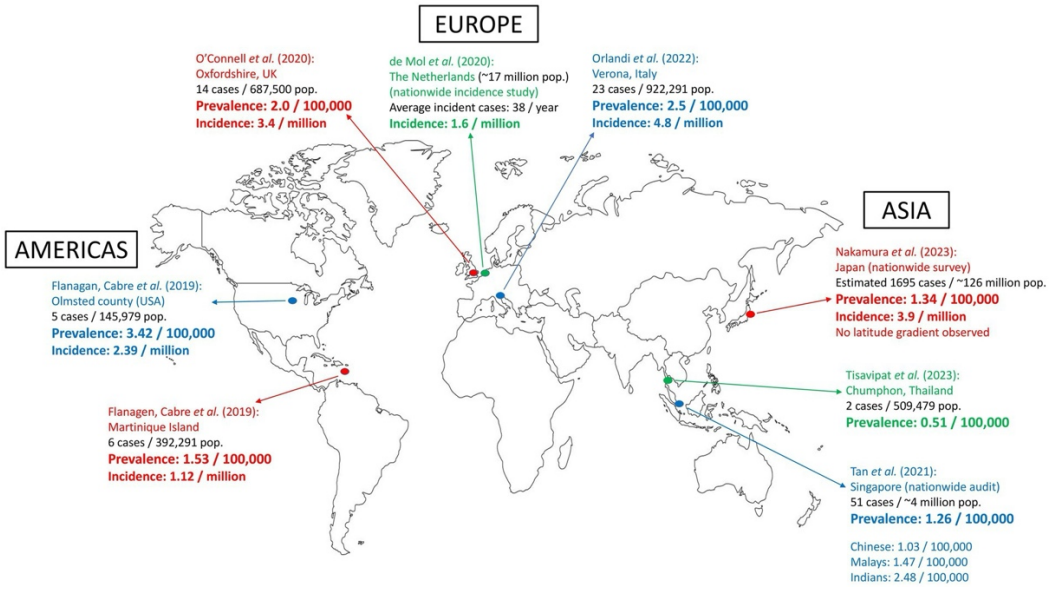

Fig. 1 World map showing population-based prevalence / incidence studies of MOGAD[11]

2.4 PATHOPHYSIOLOGY

MOG is a highly conservative glycoprotein (218 aminoacids, molecular mass of 26-28 kDa) exclusively expressed by the oligodendrocytes in the CNS of mammalians[15]. Its biological role is still under investigation; it may act as a cell adhesion molecule, regulate microtubule stability, and modulate myelin immune interactions[16]. Its location on the outermost part of the myelin sheath in the CNS makes it a potential target for MOG antibodies. These induce demyelination in EAE animal models immunized with MOG[17]. However, human MOG-IgGs do not usually cross-react with rodent MOG, making studies of animal models more challenging. The pathogenetic role of MOG-IgG is still unclear, although it was observed that a small proportion of MOG-IgG that cross-react to MOG rodent epitopes induced a MOGAD-like disease in murine models[18].

To date, it is hypothesized that the pathogenetic cascade begins in the periphery through an unknown mechanism of loss of self-tolerance (Fig. 2). In the CNS, binding between MOG-IgG and myelin may induce the incretion of IL-6 and B-cell activating

factor (BAFF), with subsequent recruitment of CD4+ T cells and macrophages that are targeted against neurons and oligodendrocytes. Complement activation might play a role in the inflammatory process: in pathology samples, complement deposition with antibody-dependent cellular phagocytosis has been observed; moreover, MOGAD patients show higher activation of both classic and alternative complement pathways compared to healthy controls[19]. Moreover, in animal models MOG IgGs cause demyelination by activating the neonatal Fc-receptor pathway, which promotes the activation of T lymphocytes and their infiltration in the CNS[20].

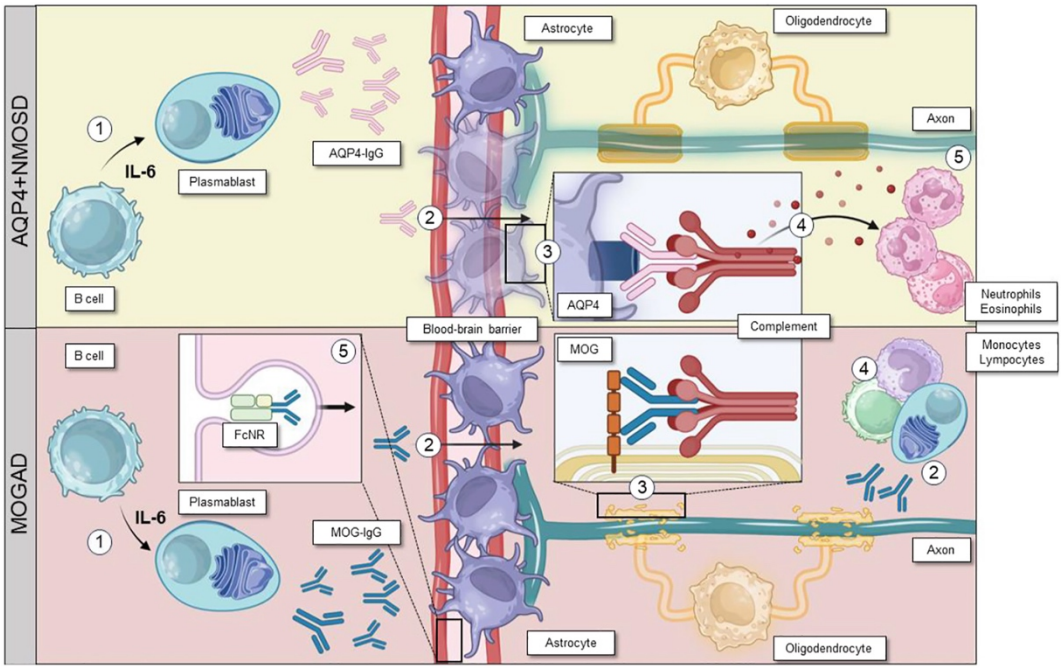

Fig. 2 - NMOSD-AQP4 and MOGAD pathogenesis[21]

2.5 NEUROPATHOLOGY

Two recent studies on human pathology of MOGAD, investigating the characteristics of brain lesions on biopsies or autopsies, have provided insights on the pathogenetic mechanisms involved in the disease[22,23]. It has been observed the presence of coexisting perivenous and confluent demyelination, and an overlap with pattern II MS pathology. Cortical demyelination is frequent, and intracortical demyelinating lesions predominate, topographically associated with meningeal inflammation. Cellular infiltrates are predominantly CD4+ T cells and granulocytes, as opposed to the preponderance of CD8+ T cells of MS lesions. Complement deposition is also observed. In opposition to NMOSD-AQP4, astrocytopathy is not a prominent feature, and the expression of AQP4 is preserved.

2.6 CLINICAL FEATURES

The different clinical features of MOGAD attacks can occur in isolation or in various combination; the frequency of the involved anatomical areas and the related symptoms is variable among adults and children.

2.6.1 OPTIC NEURITIS

Optic neuritis (ON) is the most common clinical presentation in adolescence and in adulthood, accounting for up to 50% of MOGAD cases[24]. It is rarer in pre-pubertal patients (up to 25% of cases[25]). ON is associated with a higher relapse risk compared to other clinical manifestations[26,27]. Visual loss at nadir can be severe, and 50-84% of patients can experience bilateral simultaneous involvement of the optic nerve[28,29]. At follow-up, recovery from ON is complete or almost complete, with a better response to corticosteroid treatment compared to NMOSD-AQP4 and MS, although 6-12% of cases show a permanent visual loss (visual acuity ≤20/200) in the involved eye[24]. Optic disc edema at fundoscopy is a rare event in NMOSD-AQP4 and MS, while it has been observed in up to 90% of MOGAD patients[24].

Up to 50% of adult MOGAD patients experience recurrent ON, which might represent the sole manifestation of the disease. A smaller proportion of subjects (16%) may develop a steroid-dependent chronic form of ON (Chronic Relapsing Inflammatory Optic Neuropathy – CRION)[28].

MYELITIS

The clinical picture of myelitis is characterized by acute/subacute onset of motor, sensory and/or autonomic symptoms that prompt an involvement of the spinal cord. It occurs in 20% to 40% of adult and 15% to 20% of pediatric MOGAD[30]. In some cases, it can be preceded by an infectious trigger or a vaccination[26,27]. Although myelitis symptoms may be moderate to severe at nadir, recovery is often satisfying, with a good response to steroid treatment. However, up to 6-7% of patients will require the use of wheelchair at follow-up, and 50% of subjects will experience a residual bowel/bladder dysfunction[31]; the occurrence of this manifestation is related to the

frequent involvement of conus medullaris and cauda equina in MOGAD patients (11-41%)[32].

The clinical features of myelitis that can suggest a diagnosis of MOGAD compared to NMOSD-AQP4 and MS are the male predominance, an earlier age at onset, a prodromal infectious episode or the concurrence of myelitis in the spectrum of ADEM. Moreover, up to 20% of MOGAD patients fulfill the criteria for acute flaccid myelitis with areflexia, reflecting the involvement of the anterior gray matter[32].

ACUTE DISSEMINATED ENCEPHALOMYELITIS

ADEM, a heterogeneous immune-mediated syndrome characterized by encephalopathy and polyfocal neurological signs with neuroimaging abnormalities, is the most frequent manifestation of MOGAD in pediatric patients (20-60%), especially in those aged younger than 12 years. It is rarer in adults, occurring in up to 5% of patients[30]. Moreover, up to 60% of children with ADEM test positive for MOG-IgG[26]. In 40% of MOGAD patients with ADEM it has been observed some residual cognitive impairment, including difficulties in learning and concentration[26]. Furthermore, ADEM in MOGAD is associated with a higher risk of post-ADEM epilepsy[30].

CORTICAL ENCEPHALITIS

Cortical encephalitis is a recently described MOGAD phenotype characterized by clinical manifestations - including headache (70-80%), seizures (up to 85%), fever (up to 45%) – and typical T2-FLAIR cortical hyperintensity with corresponding leptomeningeal or cortical gadolinium enhancement (FLAIR-hyperintense Lesions and Anti-MOG associated Encephalitis with Seizures – FLAMES)[33]. It occurs in 7% of all patients, being more common in children than in adults. It is often associated with short-term MOGAD relapses[34]. Hence, the evidence of seizures associated with ON or other focal manifestation should prompt MOG-IgG testing.

BRAINSTEM/CEREBELLAR SYNDROME

Signs and symptoms suggestive of an infratentorial involvement rarely occur, while they often are part of ADEM. The most frequent symptoms are represented by ataxia (45%) or diplopia (26%). In up to 40% of cases there is evidence of asymptomatic infratentorial lesions[35]. Area postrema syndrome is rare compared to NMOSD-AQP4[36(p3)].

OTHER CLINICAL MANIFESTATIONS

Other less common phenotypes have been reported in patients with MOG-IgG, although the attribution of novel clinical features to MOGAD should be regarded with caution owing to the potential risk of false positive MOG-IgG test result, especially at low titers.

1. Overlapping syndromes of MOGAD and anti-NMDAR encephalitis have been described, with clinical features that are atypical for classical anti-NMDAR disorder, such as cerebellar, brainstem and even spinal cord involvement[37]. Hence, MOG-IgG testing in anti-NMDAR encephalitis with atypical features is suggested, particularly considering that double antibody positivity is associated with a worse prognosis and, therefore, the likely need for a more aggressive immunosuppressive treatment.
2. Cranial nerve involvement, especially of trigeminal and facial nerves, have rarely been reported[38].
3. Peripheral nervous system involvement with extension to the spinal cord and cauda equina nerve roots is described[39], while further studies are needed to clarify the existence of MOG-IgG positivity in pure peripheral neuropathies.

2.7 CLINICAL COURSE

Several cohort studies have shown that disease course is heterogeneous. 40-50% of MOGAD patients have a monophasic course, while the remaining are affected by relapses[26,40,41]. Most of the available studies have shown that a higher MOG-IgG titer at onset and its persistence over time is associated with a higher risk of relapse; however, relapses can also occur in patients that become seronegative. Moreover, a monophasic course has been observed even in patients with persistently high MOG-IgG titers, making the prediction of the disease evolution over time even more challenging[42,43].

A significant proportion of MOGAD patients develops permanent disability, more frequently in adults (50-80%)[44] than in children (20-30%)[45]. In up to 60% of these patients, disability is subsequent to the onset attack, while in 40% it is due to relapses[26].

2.8 BIOMARKERS

2.8.1 MOG-IgG TESTING

The assessment of MOG-IgG positivity with a reliable assay is essential for a correct diagnosis and to minimize the risk of false positive results. It has been demonstrated that the only biologically relevant anti-MOG antibodies are those that identify MOG epitopes in their natural conformation[46]. However, early studies employed Western blotting techniques, which identify denatured MOG antigen, or ELISA, which detects linear peptides; these methods were unable to differentiate specific antibodies against the conformational epitopes of MOG antigen[7]. More recently, the development of CBAs utilizing transfected cells has allowed the identification of MOG-IgG in a clinically relevant context[47]. Multicenter validation studies have shown a high specificity for these assays (up to 99%), while the assessment of sensitivity is still limited by the absence of a reference standard for comparison. Of note, CBAs that use fixed transfected cells have a slightly lower specificity (98%) compared to live CBAs[48,49].

Serum is preferred specimen type for MOG-IgG testing. However, recent studies have suggested a role for cerebrospinal fluid (CSF) testing in MOGAD, as concomitant detection of MOG-IgG in serum and CSF occurs in 41% to 87% of patients[50,51]. CSF-isolated positivity is observed in 3-29% of cases; hence, in the appropriate clinical context, CSF testing for MOG-IgG should be undertaken, as suggested by the recently proposed diagnostic criteria (see below)[5].

Serial MOG-IgG testing could play a role in the prognostic evaluation of MOGAD patients, as described before.

2.8.2 CEREBROSPINAL FLUID ANALYSIS

CSF shows pleocytosis (predominantly lympho- and monocytes) in more than 50% of MOGAD patients. Neutrophils are detected in approximately 50-55% of patients, while they hardly ever occur in CSF of MS patients[52,53(p2)]. CSF-restricted oligoclonal bands (OCBs) are rare in MOGAD (10% of patients). On the contrary, blood-brain

barrier damage is more frequent and more severe in MOGAD than MS patients, and the albumin quotient is elevated in up to 50% of cases, while it is normal in 90% of MS subjects.

2.8.3 OTHER BIOMARKERS

During relapses, the cytokine profile of MOGAD patients show predominance of Th17-related cytokines such as IL-6, IL-8 and IL-17, similarly to the evidence from NMOSD-AQP4 cases[54]. On the contrary, a prevalent Th1-related cytokine pattern is observed in MS[55].

CSF and serum levels of glial fibrillary acidic protein (GFAP), a marker of astrocytic damage, are generally lower in MOGAD compared to AQP4-IgG+NMOSD, which is in line with the different antibody cell target (oligodendrocyte vs. astrocyte).

CSF levels of neurofilament light chain are increased during relapses in MOGAD, NMOSD-AQP4 and MS, and especially at onset, suggesting indirect neuronal damage in all the conditions[56].

2.9 OPTIC COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is an essential tool for diagnostic evaluation of MOGAD patients – given that ON is the most common manifestation – and for the differential diagnosis with NMOSD-AQP4 and MS. It uses infrared light waves that reflect off the internal microstructure of biological tissues to produce images based upon the differential optical reflectivity. OCT provides a noninvasive way to image the retina at high resolution. During an acute attack of ON, the peripapillary retinal nerve fiber layer (pRNFL) is often significantly thickened compared to MS patients[57]. After 3-6 months from the attack, progressive thinning of the pRNFL and the macular ganglion cell and inner plexiform layer (mGCIPL) is observed. Compared to NMOSD-AQP4 ON, in which severe thinning of these layers is apparent since the first attack, in MOGAD the manifestation occurs after recurrent attacks. However, some studies have shown similar entities of pRNFL and mGCIPL thinning between MOGAD and NMOSD-AQP4, notwithstanding the more severe clinical outcome expected after ON in NMOSD-AQP4 patients. The cause of the discrepancy between OCT findings and clinical impairment in the two diseases is still debated: it has been suggested that,

being NMOSD-AQP4 primarily an astrocytopathy, the pathophysiology of the disease might be related to more severe retinal dysfunction[56].

2.10 DIAGNOSTIC CRITERIA

In January 2023, the International criteria for diagnosis of MOGAD were published[5]. These criteria – proposed by an international panel of expert – represent a key step for the unification and standardization of MOGAD diagnosis.

The proposed diagnostic criteria require the following (Fig. 3)

1. A core demyelinating event, including optic neuritis, transverse myelitis, ADEM, cerebral monofocal or polyfocal deficits, brainstem or cerebellar deficits, cerebral cortical encephalitis, often with seizures.
2. A *clearly positive* serum MOG-IgG testing, defined as MOG-IgG measured by fixed CBA with a titer ≥1:100 or live CBA with a standardized method (clear positivity according to the individual assay cutoffs)

   In cases where serum MOG-IgG titer is low positive, positive without a reported titer, or seronegative but with a clear CSF MOG-IgG, at least one additional supportive clinical or magnetic resonance imaging (MRI) feature is required along with a seronegative aquaporin 4 (AQP4)-IgG test to fulfill this criterion (see Fig. 3).
3. patients should be diagnosed with MOGAD after alternative diagnoses have been excluded (including MS), as well as the McDonald criteria recommend that, before diagnosing MS, alternative diagnoses should be ruled out.

<table>
<tr><th colspan="4">Diagnosis of MOGAD (requires fulfilment of A, B, and C)</th></tr>
<tr><td>(A) Core clinical demyelinating event</td><td colspan="3">Optic neuritis*
Myelitis†
ADEM‡
Cerebral monofocal or polyfocal deficits§
Brainstem or cerebellar deficits¶
Cerebral cortical encephalitis often with seizures||</td></tr>
<tr><td rowspan="4">(B) Positive MOG-IgG test</td><td rowspan="4">Cell-based assay: serum**</td><td>Clear positive††</td><td>No additional supporting features required</td></tr>
<tr><td>Low positive‡‡</td><td rowspan="3">• AQP4-IgG seronegative AND
• ≥1 supporting clinical or MRI feature</td></tr>
<tr><td>Positive without reported titre</td></tr>
<tr><td>Negative but CSF positive§§</td></tr>
<tr><td rowspan="3">Supporting clinical or MRI features</td><td colspan="2">Optic neuritis</td><td>• Bilateral simultaneous clinical involvement
• Longitudinal optic nerve involvement (> 50% length of the optic nerve)
• Perineural optic sheath enhancement
• Optic disc oedema</td></tr>
<tr><td colspan="2">Myelitis</td><td>• Longitudinally extensive myelitis
• Central cord lesion or H-sign
• Conus lesion</td></tr>
<tr><td colspan="2">Brain, brainstem, or cerebral syndrome</td><td>• Multiple ill-defined T2 hyperintense lesions in supratentorial and often infratentorial white matter
• Deep grey matter involvement
• Ill-defined T2-hyperintensity involving pons, middle cerebellar peduncle, or medulla
• Cortical lesion with or without lesional and overlying meningeal enhancement</td></tr>
<tr><td colspan="4">(C) Exclusion of better diagnoses including multiple sclerosis¶¶</td></tr>
</table>

Fig. 3 - Proposed diagnostic criteria for MOGAD[5]

The new criteria are strongly dependent on the presence of MOG-IgG positivity to diagnose MOGAD, although the accuracies of MOG-IgG testing depend on the assay used for detection, as described before. Moreover, the dependence on the presence of MOG-IgG precludes the existence of "seronegative" MOGAD, despite the evidence of cases switching from a negative to a positive titer and vice versa. These observations reinforce the need to be guided by clinical judgment when interpreting MOG-IgG results[58].

Recently, accuracy of MOGAD criteria has been evaluated in real-world cohorts of patients[59,60]. Sensitivity ranged from 97 to 100%, while specificity ranged from 55.5 to 100%. Overall, the accuracy of these criteria increased over the previous recommendations on MOGAD diagnosis proposed by an International Panel of experts in 2018[61,62].

3. MULTIPLE SCLEROSIS: AN OVERVIEW

3.1 EPIDEMIOLOGY

MS is an immune-mediated chronic demyelinating disease of the CNS, whose pathogenetic hallmarks are inflammation and neurodegeneration. It is a multi-factorial disorder, driven by a complex interplay of genetic and environmental factors that are still under investigation.

MS is the leading global cause of nontraumatic disability among young people, and its worldwide prevalence is rising and estimated in 2.9 million cases[63] (Fig. 4). A latitude gradient for MS prevalence has been observed, with the disease becoming more frequent from the equator to the poles, although deviations from this model were described for some regions of Italy[64] and Oceania[13].

The age at onset is variable according to the clinical phenotype: for relapsing-remitting MS (RRMS), accounting for 85-90% of MS cases, mean age at onset is 30 years; for primary progressive MS (PPMS) (10-15% of MS patients), it is 40 years[65]. In 10% of cases, the disease onset occurs during infancy or adolescence[66]. The female-to-male prevalence ratio is 3:1[65].

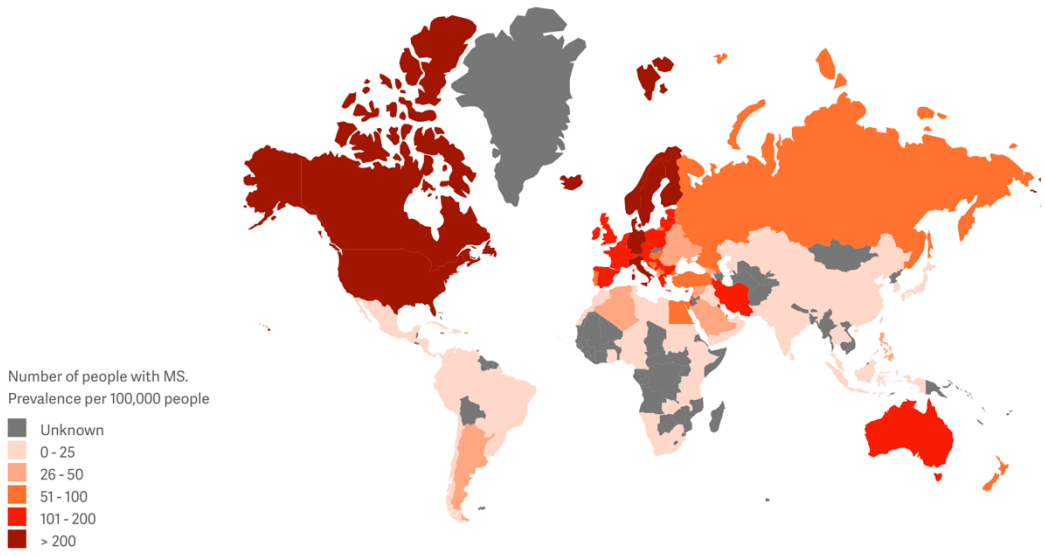

Fig. 4 - Worldwide prevalence of MS in 2020

MS symptoms are the direct cause of death in more than 50% of patients; according to recent studies, life expectancy for MS patients is approximately 7 years shorter compared with the general population, although a rise in MS survival has been observed over the last 6 decades[67].

3.2 RISK FACTORS

The cause of MS has not been determined yet. Genetic, environmental and immunologic factors are deeply intertwined in the etiology of this complex disease.

A genetic predisposition has been postulated given the fact that the prevalence of familial MS is approximately 13% for all disease phenotypes; moreover, the risk of recurrence within families increases with higher degrees of relatedness and the sharing of genetic material (35% in monozygotic twins, 6% in dizygotic twins, 3% in siblings)[68]. Genes of HLA complex represent the strongest genetic risk factor for MS, with the HLA-DRB115:01 variant of class II HLA gene being associated with an increased risk; on the contrary, the HLA-A02 variant of class I HLA gene is protective[69].

Many environmental risk factors have been associated with MS, including vitamin D, obesity, smoking and infectious agents[70]. Among the latter, Epstein-Barr virus (EBV) shows the strongest association with MS from several observations over the last decades[71]. Recently, a pivotal study has demonstrated that MS risk is minimal in individuals who are not infected with EBV and that it increases over 30-fold following EBV infection[72]. This evidence postulates a causative role for EBV in the development of MS.

3.3 IMMUNOPATHOGENESIS

MS immunopathogenesis is characterized by a complex interaction of activated immune cells of both the innate and adaptive immune system. It has been postulated that, besides the involvement in relapse-related inflammation, the immune system could play a significant role in mechanisms that lead to disease progression, as observed in a recent retrospective study in which early suppression of immune cells in the disease course was associated with reduced long-term disability[73].

3.3.1 ADAPTIVE IMMUNITY

CD4+ and CD8+ T cells. The role of CD4+ T cells in MS pathogenesis have been extensively demonstrated, with particular emphasis on IFNγ-producing Th1 cells and IL-17-producing Th17 cells, which are found in active MS lesions and are required for the development of EAE.

CD4+ T cells are involved in the activation and maturation of CNS-resident microglia and in targeting astrocytes; Th17 cells contribute to disrupting the blood-brain barrier, thus promoting neuroinflammation[74]. Recently, it has been observed that β-synuclein-reactive CD4+ T cells, which can migrate to gray matter and directly damage neurons, are associated with neuronal decline and neurodegeneration[75].

CD8+ T cells are predominant in the inflammatory infiltrates of MS plaques. Their presence has been assessed in both active and chronic active MS lesions, as well as in meningeal MS infiltrates[76].

B cells. B lymphocytes also play a role in the pathogenesis of this disease, as suggested by the significant results obtained from therapies targeting B lymphocyte depletion using anti-CD20 treatments. It is known that patients with MS exhibit abnormal production of Ig within the CNS, as demonstrated by the frequent presence of CSF-restricted OCBs. Moreover, clonally expanded B cells or their immunoglobulin products in the CSF, meninges and brain parenchyma of patients with MS have been observed in several studies. Recently, single-cell B cell receptor sequencing of B cells in blood and CSF from MS patients has shown a cross-reaction of antibodies generated in response to EBNA1 with glial cell adhesion molecule (GlialCAM), a protein expressed by CNS-resident glial cells, strongly suggesting that EBV infection can directly induce autoantibody production in patients with MS[77].

3.3.2 INNATE IMMUNITY

Unconventional T cells, including γδ T cells and mucosa-associated invariant T cells (MAIT), are involved in the pathogenetic cascade of MS, with their production of IL-17 considered to be key to their pathogenesis.

Monocytes and macrophages. In MS lesions, macrophages play multifaceted roles based on their polarization state. Macrophages in the CNS alter their phenotype, affecting ATP production, phagocytic capacity, and reactive species production. Pathogenic monocyte subsets producing IL-1β and CXCL10 promote immune cell recruitment into the CNS during EAE.

Dendritic cells. Conventional dendritic cells exhibit a dysregulated pro-inflammatory phenotype, facilitating migration to the CNS. Monocyte-derived dendritic cells can infiltrate the CNS under inflammatory conditions, essential for inducing TH17

cells and CNS inflammation in EAE. IL-12 production by DCs promotes TH1 and cytotoxic CD8+ T cell expansion, considered pivotal in MS pathogenesis[76].

3.3.3 MICROGLIA

Microglia are considered to play a crucial role in tissue homeostasis and inflammation; it is suggested that in MS, an imbalance between their activation and interactions with peripheral immune cells versus dormancy might favor an activated, tissue-destructive role[76].

3.3.4 EARLY STAGES OF THE DISEASE

The aberrant activation of T cells in MS is based on the presentation of antigens - whose nature is still under investigation - by B lymphocytes and cells of the myeloid lineage (macrophages, dendritic cells, and microglia) within the CNS and in the periphery due to loss of self-tolerance. CNS was once considered immune-privileged, meaning CNS antigens were thought to escape immune detection due to a lack of connection to cervical lymph nodes. This view changed with the discovery of an intracranial lymphatic network, located in the dura mater, which plays a role in fluid and lipid homeostasis, waste removal, and immune coordination[78]. During inflammation, changes in the expression of chemokines facilitate APC migration through the lymphatic system, impacting the immune response.

In early RRMS, widespread inflammatory infiltrates consisting of CD4+ T cells, CD8+ T cells, B cells, and monocytes are observed. These cells destroy myelin-producing oligodendrocytes, forming acute lesions primarily in white matter (WM) but also in grey matter (GM). This results in demyelinated axons, axonal damage, and neuronal loss – a hallmark of disease progression – occurring even in the early stages in the disease[76].

3.3.5 LATE STAGES OF THE DISEASE

Neuronal loss is a key factor in physical disability and disease progression, yet the precise involvement of the immune system (both infiltrating and resident) in this process is still under investigation. Neuropathological and MRI studies reveal that while new focal inflammatory lesions decrease with age and disease duration, chronic

active lesions with activated microglia and myelin-containing macrophages are common in progressive MS. Chronic inactive lesions, which lack these immune cells, become more frequent but smaller in size over time in the brains and spinal cords of patients with progressive disease[79,80]. Moreover, inflammatory infiltrates of B cells and CD8+ T cells form aggregates in the leptomeninges, resembling tertiary lymphoid follicles seen in other chronic inflammatory diseases. These follicles may result from unresolved chronic inflammation. In progressive MS, cortical lesions increase in frequency near meningeal inflammation, with specific neurons in the upper cortical layers showing stress pathway activation. Soluble factors produced by immune cells may diffuse into the brain parenchyma, triggering microglia activation and subsequent tissue injury[76].

3.4 CLINICAL MANIFESTATIONS AND DISEASE COURSE

3.4.1 CLINICAL MANIFESTATIONS

The clinical picture of MS is heterogeneous and depends on the localization of demyelinating lesions within the CNS. Although no clinical pattern is pathognomonic for MS, some presentations are highly associated with the disease. Typically, MS onset is characterized by an *initial demyelinating event* (IDE) in 85% of patients; an IDE consists of an episode of acute neurological disturbance resulting from a demyelinating lesion in various locations, including the optic nerve, spinal cord, brainstem/cerebellum, or cerebral hemispheres. If the IDE is accompanied by additional distinctive features of MS, it is referred to as clinically isolated syndrome (CIS)[81].

The most relevant clinical manifestations of MS include

- ON, representing the clinical onset in up to 25% of cases and occurring in up to 70% of patients during the disease course. ON is associated with a conversion from CIS to MS in 34-75% of patients[82];
- sensory symptoms, representing the clinical onset in up to 40% of patients. These symptoms are typically expression of spinal cord or brainstem lesions[83];
- motor symptoms. They represent the initial symptom in 30-40% of patients; corticospinal tract alterations can occur both in the context of a relapse and in the progressive phase[83];

- brainstem and cerebellar symptoms in up to 70% of MS patients;
- bowel and bladder symptoms. These manifestations tend to parallel that of motor disturbance in the lower limbs and become permanent in late MS, affecting 34-99% of patients. Patients most commonly complain of urinary urgency, but hesitation, polyuria, and incontinence can also occur. Constipation is more frequent than fecal incontinence. Men with MS frequently experience erectile dysfunction and impotence[82];
- fatigue. This symptom is experienced by 75-90% of MS patients, and is not associated with disease severity. It is defined as a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities[84];
- cognitive impairment: see "5. Cognition in MOGAD and Multiple Sclerosis".

Each of the seven functional systems (FS) described above is included in the Expanded Disability Status Scale (EDSS), a complex score that reflects the extent of disability in patients with MS, as well as the evaluation of ambulation ability. Scores range from 0 to 5 or 6 depending on the functional system, which are then combined to form the overall EDSS score ranging from 0 (no neurological disability) to 10 (death due to MS). Patients with EDSS score up to 5 are fully ambulatory patients. Up to this point, the main determinant of EDSS are FS, while the ambulation status is the main determinant in the degree of disability after 5[85].

3.4.2. DISEASE COURSE

The disease course is heterogeneous and variable over time, but it is mainly characterized by transient periods of neurological worsening (relapses), progressive neurological deterioration or a combination of the two[86]. A relapse is defined as a monophasic acute/subacute clinical episode lasting at least 24 hours (usually days or weeks), with patient-reported symptoms and objective signs that are suggestive of an inflammatory event of the CNS. Relapses tend to recovery in many cases, but they can also leave permanent disability after resolution of the inflammation. Relapsing-remitting MS (RRMS) is the most prominent clinical phenotype at onset and is accompanied by new or expanding CNS demyelinating lesions, the pathological hallmark of the disease. Over time, the development of permanent neurological deficits and the progression of clinical impairment become prominent, with an evolution towards

secondary progressive MS (SPMS). Around 10-15% of patients show a progressive course since the disease onset (primary progressive MS, PPMS), with gradual clinical worsening which is mostly independent from any eventual concurrent relapse. The disease is defined *active* when there is evidence of clinical relapse and/or of new or expanding demyelinating lesions at MRI scans[87] (Fig. 5).

A CIS is defined as an IDE suggestive for MS which does not fulfill the criteria of dissemination in space (DIS) or in time (DIT) which are required for MS diagnosis (see below).

The term radiologically isolated syndrome (RIS) identifies the incidental occurrence of MRI lesions suggestive of an inflammatory demyelinating process in a subject without clinical signs and symptoms suggestive of IDE. Signs of new or enlarged T2 lesions – as well as gadolinium-enhancing lesions - or presence of OCBs at subsequent MRI scans are related to an increased risk of developing MS in the future[88].

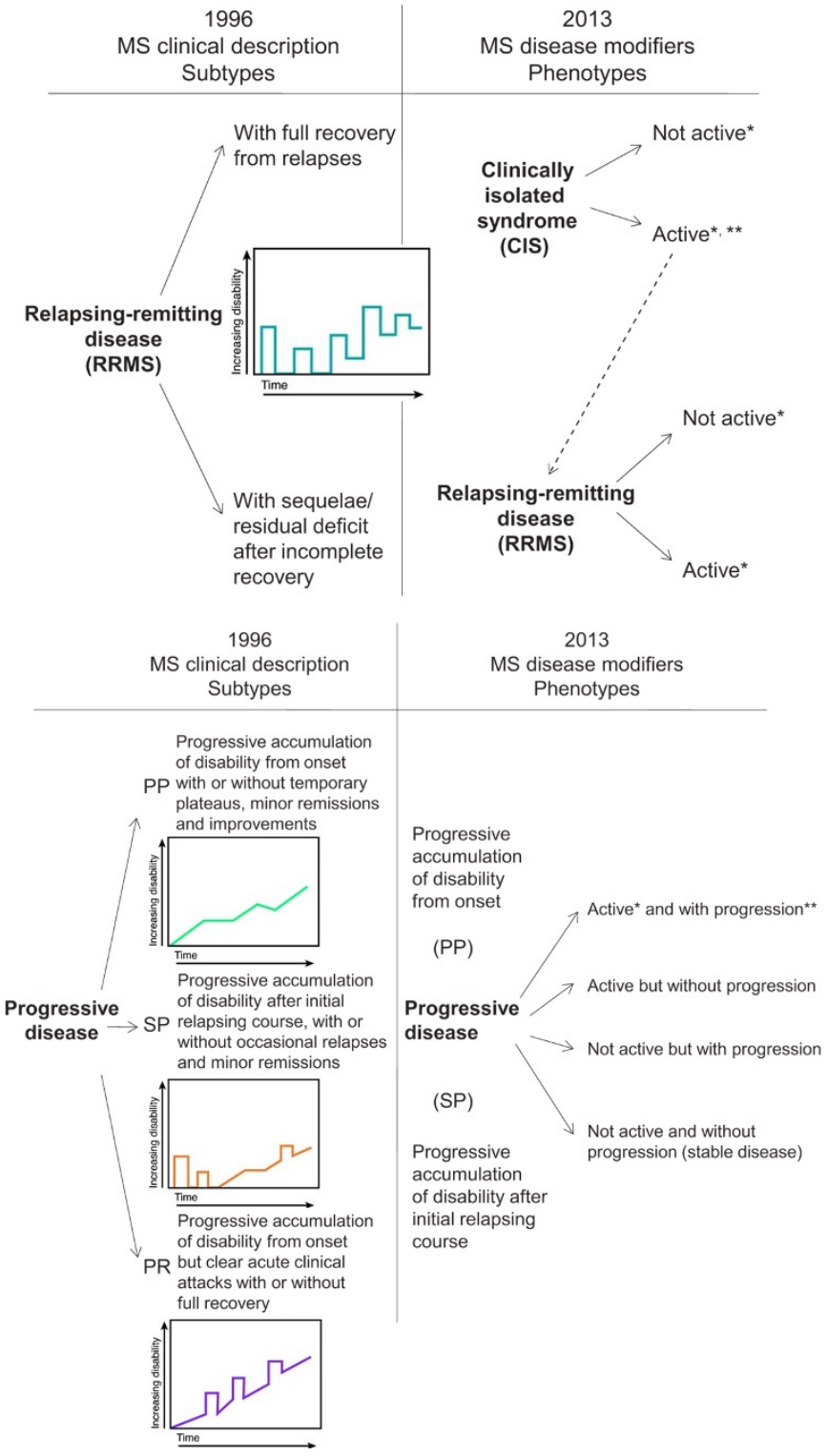

Fig. 5 - Clinical MS phenotypes according to 1996 and 2013 descriptions[87]

3.5 DIAGNOSTIC CRITERIA

Diagnostic criteria are essential in a complex and heterogeneous disease like MS, which lacks a single pathognomonic biomarker to establish the diagnosis. Currently, the universally utilized "McDonald Criteria," proposed by the International Panel on Diagnosis of MS in 2001[89] and subsequently revised in 2005, 2010 and 2017[86], integrate neuroimaging findings from MRI with clinical and paraclinical diagnostic elements to objectively demonstrate spatial and temporal dissemination of lesions. McDonald Criteria enable early diagnosis of MS with high sensitivity and specificity, improving patient counseling and early treatment (Fig. 6 and Fig. 7).

Compared to the 2010 iteration, the revised criteria proposed in 2017 include the following updates:

- In individuals with CIS and clinical-radiological evidence of DIS, the presence of OCBs in CSF, in the absence of other CSF findings abnormal for MS, allows for a diagnosis of the disease.
- Symptomatic lesions: including symptomatic lesions for determining DIS and DIT does not affect the diagnostic specificity of MS. Therefore, the Panel recommended their inclusion for both criteria for RRMS and PPMS.
- Cortical and juxtacortical lesions: neuropathological studies have highlighted the presence and importance of cortical lesions in MS. Despite variability in MRI standards for recognizing cortical lesions, the Panel considered that, in conjunction with presence of juxtacortical lesions, cortical lesions may also contribute to demonstrating DIS.

	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)	None*
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis. An attack is defined in panel 1. *No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered. †Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed. ‡The MRI criteria for dissemination in space are described in panel 5. §The MRI criteria for dissemination in time are described in panel 5. ¶The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

Fig. 6 - 2017 revision of McDonald Criteria for relapsing-remitting MS diagnosis[86]

Primary progressive multiple sclerosis can be diagnosed in patients with:

- 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse

Plus two of the following criteria:

- One or more T2-hyperintense lesions* characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial
- Two or more T2-hyperintense lesions* in the spinal cord
- Presence of CSF-specific oligoclonal bands

*Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required.

Fig. 7 - 2017 Criteria for the diagnosis of Primary Progressive MS

3.6 BIOMARKERS: CSF ANALYSIS

CSF analysis has regained a role in the diagnostic pathway of MS after the inclusion of OCB as a tool to obtain DIT according to the latest revision of diagnostic criteria. This is due to its good diagnostic accuracy and the increasing challenge of misdiagnosis when MS diagnosis relies excessively on MRI data. Given that MS is considered an inflammatory disease of the CNS with focal blood-brain barrier (BBB) damage, alterations in measurable markers in the CSF are plausible. Among these, the most clinically relevant are elevated leukocyte count as an indicator of inflammation and concentrations of total protein and albumin as markers of BBB disruption.

In approximately half of MS patients, leukocyte count increases up to 50 cells/mm^3. Markedly higher pleocytosis is observed in only 1-2% of MS cases, which should prompt consideration of alternative diagnostic hypotheses, particularly infectious etiologies or NMOSD. Approximately 90% of cells are lymphocytes (90% T cells and 10% B cells) in MS. Typically, there is no hypoglycorrhachia in MS, and total protein levels or albumin ratio are generally normal, reflecting the highly focal BBB disruption seen in MS[90].

A characteristic feature of CSF abnormalities in MS is the increased intrathecal production of immunoglobulins. According to guidelines, this is demonstrated through qualitative assessment of increased IgG using the IgG index or – more recently – Kappa free light chain using the Kappa-index[91] – and qualitative detection of OCBs which are distinct in the following patterns[92]:

- Pattern 1: absence of OCBs
- Pattern 2: OCBs found exclusively in CSF – typical – but not exclusive – of MS.

- Pattern 3: OCBs found both in serum and CSF, but with some additional bands detected in CSF only – this pattern is observed not only in MS, but also in other systemic inflammatory diseases with CNS involvement (e.g.: sarcoidosis)
- Pattern 4: OCBs identical in serum and CSF (mirror pattern) – this pattern is observed in systemic inflammatory diseases
- Pattern 5: identical monoclonal band in serum and CSF – related to multiple myeloma or monoclonal gammopathy of undetermined significance.

3.7 OTHER DIAGNOSTIC BIOMARKERS

3.7.1 VISUAL EVOKED POTENTIALS

Visual evoked potentials (VEPs) exhibit high sensitivity in detecting subclinical optic nerve lesions, although they are not included in diagnostic criteria. VEPs are abnormal (with increased P100 wave latency or >10% difference between eyes with normal latencies) in approximately 30% of CIS patients and more than 50% of individuals with MS without a history of optic neuritis. The test's specificity is low, as increased latency is also observed in numerous other CNS or ocular pathologies[93].

3.7.2 OPTIC COHERENCE TOMOGRAPHY

OCT can be used to measure the thickness of the retinal nerve fiber layer, which is reduced in most patients (85%) with optic neuritis. Optic nerve or optic tract demyelination leads to retrograde degeneration of unmyelinated retinal nerve fiber layer axons. Retinal nerve fiber layer loss becomes evident with OCT approximately three months after optic neuritis[94]. OCT testing may be useful for demonstrating objective evidence of retinal nerve fiber layer loss in patients who have a history consistent with optic neuritis but otherwise have a normal examination and brain imaging.

4. DIFFERENTIAL DIAGNOSIS: NEUROIMAGING PERSPECTIVE

The differential diagnosis of MOGAD and MS is often challenging, as clinical features of these two diseases are frequently overlapping; the diagnosis is particularly complex in patients showing a low-titer positivity for MOG-IgG, which has been observed in a wide range of inflammatory and non-inflammatory neurological conditions other than MOGAD[95,96]. MRI is an invaluable tool to differentiate MOGAD from MS and to make the ultimate diagnosis. During the last few years, an increasing amount of new data regarding the specificity of observed lesions as well as the associated dynamic changes in the acute and follow-up phase in each condition has been reported in distinct studies[56,97].

4.1. OPTIC NERVE IMAGING

To effectively confirm optic neuritis and accurately identify discriminator signs, it is crucial to perform orbital MRI with fat-saturated sequences. Conventional brain MRI could be not sufficient for evaluating the optic nerve due to its limitations in sensitivity.

MOGAD ON is frequently bilateral (31-84% of cases), with extensive T2 hyperintensity (>50% of the optic nerve length), typically involving the anterior segment (including the intra-orbital segment). The chiasm and retro-chiasmal pathways are spared, contrasting with NMOSD-AQP4 where they are more frequently affected. The optic nerve is edematous, enlarged and tortuous, with possible optic disc edema. These findings are more prevalent in MOGAD-associated optic neuritis compared to NMOSD-AQP4[98]. Approximately one-third of cases exhibit optic perineuritis, described as circumferential, 'tram-track' enhancement of the optic nerve sheath, which may extend into the surrounding orbital fat, a feature not observed in MS or NMOSD-AQP4 patients[29]. These findings are helpful in differentiating MOGAD ON from MS ON, in which a unilateral, short unilateral and short lesion, involving the anterior segment of the optic nerve is more frequent[29].

Brain MRI is often normal in MOGAD-related optic neuritis cases, with rare association with typical MS brain lesions (no association in 77.2-91.5% of cases). Asymptomatic spinal cord involvement is found in 10% of cases.

During follow-up, remission of optic nerve tortuosity and contrast enhancement following high-dose corticosteroid therapy is often encountered. Subsequent orbital MRIs may reveal residual T2 hyperintensity, often associated with optic nerve atrophy (up to 90% of cases at one-year follow-up), despite good clinical recovery[99].

4.2. SPINAL CORD IMAGING

During an episode of myelitis in MOGAD, MRI can reveal spinal cord involvement in two distinct patterns:

- Longitudinally extensive transverse myelitis (LETM), characterized by hyperintense T2 lesions extending over at least 3 vertebral segments (70-80% of TM cases[32]).
- Short segment T2 hyperintense lesions, extending less than 3 vertebral segments.

Regardless of their extent, these lesions involve both GM and WM, affecting more than 50% of the axial cross-sectional area of the spinal cord, with possible spinal cord swelling. These lesions typically occur preferentially at the thoracolumbar level, often involving the conus medullaris (30-41% of cases), which is considered highly specific for MOGAD[32]. Disproportionate spinal cord gray matter involvement is often present (up to 30% of MOGAD cases), visualized as an “H” pattern in the axial plane and a linear central T2 hyperintensity in the sagittal plane. MOGAD myelitis can also be associated with “pseudo-dilatation” of the central canal within the acute lesion, mimicking physiological central canal dilatation. Contrast enhancement is more rarely observed in MOGAD than in NMOSD-AQP4 and in MS, with a heterogeneous distribution and indistinct margins ("cloud-like" enhancement), although occasionally nodular or meningeal enhancement may also be seen[100,101]. In patients with clinical suspicion of TM, a normal radiological picture of the spinal cord can be observed, albeit rarely[102].

Patients with TM show a normal brain MRI in more than 50% of cases. Non-specific WM lesions have been described in 38.9% of cases, while typical MS changes are rare in both LETM and short myelitis patterns. Additionally, a study with a mixed cohort of pediatric and adult cases observed a recurrence of ADEM-like lesions in approximately 30% of subjects with myelitis onset.

Data on radiological follow-up of MOGAD myelitis are still scarce. It has been observed that spinal cord atrophy is uncommon, as expected from the good clinical recovery that occurs in the majority of TM patients. Particularly, a study investigated the evolution of cervical cord atrophy through measurement of the average area of the C2-C7 segment among NMOSD-AQP4 or MOGAD patients compared to control subjects; significantly greater cervical atrophy was observed in NMOSD subjects, but not in MOGAD, compared to controls[103]. Complete resolution of spinal cord lesions can be seen in up to 79% of MOGAD cases[104].

Up to 90% of MS patients exhibit multiple spinal cord lesions, representing one of four typical anatomical locations for MS lesions. The cervical spine is the most frequent site (50%-60%), followed by the upper thoracic region (20%-45%), likely due to the higher concentration of WM in cervical spinal cord segments. Lesions in the lower thoracic or medullary cone regions are less common. These lesions are typically small, affecting one or two spinal cord segments, and are located peripherally (lateral or dorsal) in the axial plane. They appear hyperintense on T2-weighted images and isointense on T1-weighted images, with a wedge-shaped appearance in axial views and ovoid in sagittal views. In rare cases, lesions may extend into the central gray matter, occupying more than half of the cord's cross-sectional area. Acute spinal cord lesions in MS may exhibit focal edema and variable enhancement patterns (often nonspecific nodular or patchy enhancement). LETM is uncommon in adult-onset MS myelitis, and its presence should prompt consideration of alternative diagnoses[105].

4.3. BRAIN IMAGING

4.3.1. MOGAD

According to the heterogeneity of cerebral manifestations, brain lesions in MOGAD patients are varied. Brain lesions are observed in 42%-53% of MOGAD cases, encompassing deep gray matter lesions, cortical lesions, subcortical or juxtacortical lesions, brainstem and cerebellar lesions, large hemispheric lesions, and, infrequently, patterns resembling leukodystrophy[40]. Among these locations, lesions in the deep gray matter and large lesions in the middle cerebellar peduncles are more

frequent in MOGAD compared to NMOSD-AQP4. Diffuse involvement of the pons and/or adjacent to the fourth ventricle (anterior location) may also suggest MOGAD over AQP4+NMOSD, although this has not been consistently confirmed in all studies[35].

Typically, T2 lesions in MOGAD are limited (three or fewer) and manifest as "fluffy", poorly demarcated areas extending from the cortico-subcortical junction to the deep WM GM, either unilaterally or bilaterally. Tumefactive lesions are notably more prevalent in MOGAD (22%) than in NMOSD-APQ4 patients (5%). These brain white matter lesions pose challenges in differentiation between NMOSD-AQP4 and MOGAD, although NMOSD-AQP4 lesions tends to exhibit more frequent diffusion restriction (67%) compared to MOGAD (26%). Transient T1-hypointense lesions can occur during the acute phase of MOGAD, but chronic T1 hypointensities are less common in MOGAD patients compared to MS[106].

Gadolinium-enhancing (Gd+) lesions in MOGAD are often described as nodular or perivascular within white matter lesions, rather than the "open ring" pattern typically seen in MS. These lesions were observed in 44%-65% of NMOSD and MOGAD cases, whereas they were more frequent in MS (74%)[40]. Additionally, nonspecific leptomeningeal enhancement around the brainstem and linear cortical enhancement have been reported in these conditions[5].

Uni- or bilateral thalamic and basal ganglia lesions are more common in MOGAD than NMOSD-AQP4 and MS. During follow-up, MOGAD typically exhibits more resolution of T2 brain lesions compared to NMOSD-APQ4 and MS. Ovoid periventricular "Dawson fingers" lesions are rare in MOGAD, whereas extra callosal extension (55%) and resolution of T2 MRI lesions (56%) are more commonly observed in MOGAD compared to NMOSD and MS[107].

In MOGAD, cortical lesions typically manifest during episodes of cerebral cortical encephalitis and are visible on fluid-attenuated inversion recovery (FLAIR) images, often involving large cortical areas. This is distinct from MS, where cortical lesions may be less conspicuous on conventional sequences and are more effectively identified using advanced MRI techniques such as double inversion recovery, phase sensitive inversion recovery, or magnetization-prepared rapid gradient-echo sequences[33,108].

So far, limited studies have investigated the presence of brain atrophy in MOGAD and its clinical implications. Cortese et al. observed no differences in brain parenchymal

fraction, white matter fraction, and deep grey matter fraction among 31 RRMS, 30 NMOSD-AQP4, 30 MOGAD patients and 34 healthy controls (HC)[109]. Similar findings were observed in another less recent study including 33 MOGAD, 18 NMOSD-AQP4 patients and 61 HC[110]. Conversely, in a study involving 35 MOGAD, 38 NMOSD-AQP4, 37 MS cases and 60 HCs, Duan et al. observed cortical and subcortical GM atrophy in MOGAD cases[111]. Moreover, they found correlations between clinical disability and relapse frequency with subcortical GM volume, suggesting its potential as a disease progression biomarker. Zhuo et al. showed cortical atrophy in the frontal cortex (especially the orbitofrontal area) and temporal gyrus, as well as deep GM structures including the thalamus and hippocampus, the latter being associated with clinical disability and cognitive impairment[112]. In another study including 20 MOGAD, 19 NMOSD-AQP4, 18 RRMS patients and 18 HC, Messina et al. delved into the connection between deep GM volume and the clinical course of monophasic or relapsing MOGAD. They found that the relapsing MOGAD group exhibited lower hippocampal volumes compared to the monophasic group. Conversely, caudate volumes were notably higher in the relapsing group. However, only the difference in hippocampal volume was plausible, particularly evident in the relapsing subgroup with brain or brainstem attacks, where hippocampal volume reductions were consistent[113].

Regarding atrophy of the infratentorial structures, no significant reductions in brainstem and cerebellar volumes in MOGAD compared to NMOSD-AQP4 and MS was observed[111,112]. Zhuo et al. further proposed that there might be a relative preservation of cerebellar systems in MOGAD, characterized by milder cerebellar atrophy compared to NMOSD-AQP4.

To date, studies investigating the presence of longitudinal brain atrophy in MOGAD patients are still scarce and inconsistent owing to relatively small sample sizes and varied methodologies employed for brain volume measurements. A recent study compared brain volume changes in 22 MOGAD patients with different disease phenotypes and 22 HC, observing decreased total brain volume, GM, WM, and deep GM structures in MOGAD patients. Distinct volumetric changes were observed between patients with a relapsing course and those with a monophasic course. Specifically, during the first year of disease, relapsing patients exhibited significantly decreased volumes in total brain, deep GM, cerebellum, and hippocampus. Analysis of EDSS data revealed a significant negative correlation between EDSS scores and WM and thalamic volumes, while the number of relapses correlated with lower total brain

volume[114]. Subsequently, Lotan et al. (2023) demonstrated that volume loss in MOGAD may occur partly independent of relapses. They observed a significantly higher rate of thalamic and hippocampal volume loss in a longitudinally evaluated group of 8 relapse-free MOGAD patients. Finally, a recent study including 14 MOGAD and 32 MS patients evaluated brain volume loss over an average two-year interval, independent of clinical recurrent disease, reporting evidence of cortical and deep GM volume loss in MOGAD as well as in MS cases[115].

4.3.2. MULTIPLE SCLEROSIS

Typical brain MRI T2/FLAIR lesions are characterized by an ovoid morphology, with the maximum axis extending > 1 cm. They are preferentially located in periventricular, juxtacortical (involving U-fibers), cerebellar and brainstem areas; inferior temporal lobe is also frequently involved. Periventricular lesions tend to align perpendicular to the corpus callosum, assuming the so-called "Dawson's fingers" morphology. Large, confluent demyelinating areas several centimeters in diameter can also be observed. Gd+ lesions show a typical ring- and/or open-ring enhancement. T1-hypointensities are also frequent, and are known as black holes. Most of these lesions, if of recent onset, tend to become isointense within a few months due to remyelination and resolution of tissue edema. However, chronic hypointense T1-weighted lesions, caused by more advanced pathological substrates such as axonal loss, Wallerian degeneration, and gliotic changes, tend to persist over time. The volume of chronic black holes increases with the duration of the disease, being greater in subjects with RRMS compared to those with CIS, and in SPMS patients compared to those in RR phase[116].

MS lesions have been histopathologically characterized as forming around central veins. The central vein sign (CVS) refers to a linear hypointensity centrally located within lesions, visualized on susceptibility-sensitive MRI sequences (e.g., T2* scans), corresponding to the small vein or venule around which the lesion developed[117]. Some studies have observed a much lower proportion of CVS lesions in MOGAD compared to MS patients[109,118], suggesting that CVS could be a valuable imaging sign to differentiate MS from MOGAD.

Cortical lesions (CLs), one of the pathologic hallmark of MS, are defined as focal abnormalities completely within the cortex or spanning the cortex and subjacent white

matter[119]. Based on their morphology on MRI, CLs have been grouped into four types[120]

- round or ovoid: with sharp margins, morphologically similar to lesions of the white matter, sometimes extending throughout the entire cortical thickness;
- vermiform: following the profile of one or more gyri;
- wedge-shaped: subpial base and apex that may extend into the white matter;
- clusters of microgranular lesions: typically seen in patients with SPMS.

CLs are observed in >90% MS cases, and are more prevalent in progressive forms of the disease. These lesions have been linked to disease conversion and progression, providing insights into cognitive decline in MS. Moreover, the extent of CLs and the rate at which new CLs form predict worsening clinical disability and cognitive dysfunction in patients with multiple sclerosis (MS)[105].

Brain atrophy occurs in patients with MS from the early stages of the disease; it represent a helpful tool in differentiating disease phenotypes and providing insight into the physical disability and cognitive decline associated with the disease.

The clinical correlations of brain atrophy in MS patients have been shown since the early MRI studies. In a 1996 study involving 26 patients with RRMS and SPMS, significant brain atrophy differences were demonstrated in subjects with SPMS compared to those with RRMS[121]. Subsequent studies have shown that brain atrophy occurs in all forms of MS, from CIS to PPMS and SPMS, with more pronounced effects in the latter two forms[122].

In patients with CIS, brain and GM volume reduction has been observed within the first 9 months after clinical onset, significantly more in those who develop a second attack (clinically definite MS). GM matter loss appears to be pivotal in determining this correlation[123]. Furthermore, the degree of brain atrophy one year after CIS onset correlates with clinical disability after 6 years[124]. More recently, a study highlighted comparable brain atrophy levels between patients with RRMS and those with RIS, also documenting cognitive deficits in a quarter of the latter[125].

In clinically stable MS patients not taking disease-modifying drugs (DMDs), annual brain volume loss (BVL) is estimated at 0.5-1%, compared to 0.1-0.3% in healthy individuals[122]. Longitudinal studies across different patient cohorts have suggested

that annual BVL is not correlated with clinical phenotype[126]. A prospective study over 7.5 years provided specific annual BVL cutoffs to differentiate MS patients from healthy subjects. Specifically, MS patients (across all phenotypes) show an annual brain volume reduction of -0.57% compared to -0.27% in healthy subjects. The cutoff to maximize the difference between the two groups is -0.4%, with 80% specificity and 65% sensitivity[127].

Clinically, assessing brain atrophy is crucial as it can predict MS progression. In a multicenter prospective study, brain volume reduction and lesion burden change over one year were predictive of disability measured by EDSS scale 10 years later[128].

5. COGNITION IN MOGAD AND MULTIPLE SCLEROSIS

To date, very little data has been published regarding cognitive profile of patients with MOGAD. However, there is some evidence of a subset of patients that might suffer from cognitive impairment (CI). In a multinational survey that included 204 people diagnosed with MOGAD, patients complained of memory problems or confusion during the course of the disease in 26% and 19% of cases respectively[129]. Conversely, in a recent series of 29 patients with highly relapsing MOGAD and a median follow-up of 14 years, disability outcomes were generally favourable, with the exception of two patients that experience severe disability, including CI. One patient was reported to score 23 out of 30 on the Montreal Cognitive Assessment, with points lost in the domains of attention, visuo-construction, and memory. The second patient underwent severe disability and dementia prior to death after 24 years of disease with onset in childhood[130].

Several case reports have also reported CI in MOGAD. Particularly, Baba et al. described a 60 years-old patient with an "atypical" onset, characterized by personality changes and a nine-month history of progressive cognitive decline, particularly in memory. On admission, the patient scored 11 out of 30 on the Mini-Mental State Examination (MMSE)[131]. Another study describes a case of a 68-years old woman diagnosed with MOGAD; at admission, she scored 23/30 on the Korean MMSE, with impairment in orientation, memory, attention, and visual construction. Brain MRI scan showed multifocal hyperintense lesions in the cortical, subcortical, periventricular white matter which decreased in volume after two weeks. After multidisciplinary rehabilitation, at discharge she performed 30/30 at MMSE[132].

Three studies have provided detailed cognitive profiles in MOGAD. In a retrospective chart review of 9 adult MOGAD patients (median age 33 years), deficits in verbal memory, visual memory, confrontation naming, verbal fluency, auditory working memory, visuospatial abilities, processing speed, and executive function (specifically set shifting and concept formation) were observed. Overall, 44% of these cases demonstrated impaired performances (below the 5th percentile) in at least one cognitive domain. Of note, 8 of 9 patients had experienced an encephalitis attack during the disease course[133].

In another study, a cohort of 12 pediatric-onset relapsing MOGAD patients and 12 age-matched HC performed the Penn Computerized Neurocognitive Battery[134],

showing significantly slower response times and poorer performances in the Complex Cognition domain (including language and nonverbal reasoning) compared to HC.

Tan et al. described a case series of 7 pediatric MOGAD patients, observing generally intact performances with mild deficits in processing speed, executive function (notably on parent-reported questionnaires), and visual-motor/fine motor skills. They also reported attention difficulties, primarily based on poor performances on Part A of the Trial Making Task, a task likely reflecting psychomotor/processing speed issues[135].

Furthermore, in a retrospective study on 76 children with MOGAD, 20 had academic difficulties during the last follow-up (mean follow-up of 4 years and 7 months), particularly those with younger age of onset (<10 years), clinical presentation of ADEM, and involvement of deep grey matter and putaminal lesions[136]. Hence, cognitive deficits in pediatric-onset MOGAD may have long-term implications for academic outcomes.

Finally, Zhuo et al. explored a possible relationship of CI with structural and volumetric brain changes in a study involving 17 MOGAD, 20 NMOSD-AQP4 patients and 28 HC. It was observed that, in MOGAD group, GM volume in left hippocampus/parahippocampal gyrus negatively correlated with EDSS and positively correlated with California Verbal Learning Test score. Moreover, GM volume in right superior temporal gyrus/insula positively correlated with MoCA.

CI has been described in MS since Charcot in 1877; however, research in the 20th century primarily focused on physical disability, as evidenced by the limited number of rigorous studies focused on assessing cognitive function. Over the past three decades, CI has been more extensively investigated and are now recognized as a prominent feature of MS, negatively impacting physical autonomy and activities of daily living. Nevertheless, the exact mechanisms underlying CI in MS remain unknown, and effective therapies for this aspect of the disease are lacking.

CI is highly prevalent in MS, affecting 34–65% of patients during the disease. Cognitive deficits can manifest in every stage of MS, including RIS. CI can progress gradually or abruptly during relapses, and in recent years, isolated cognitive relapses involving exclusively cognitive performance have been documented. Overall, the frequency and severity of CI tend to worsen over time, particularly in progressive MS

courses. Studies estimate that cognitive dysfunction occurs in approximately 20–25% of CIS and RIS, 30–45% in RRMS, and 50–75% in SPMS[137,138]. However, it has been demonstrated that the primary factors associated with CI are greater physical disability, as assessed by EDSS, and older age, rather than longer disease duration or the specific course of MS itself[139].

Various cognitive domains may be affected in MS patients, including attention, executive functions, working memory, information processing speed, and long-term memory. Visuospatial disturbances and impairment in social functioning may also be observed[137]. Recently, five phenotypes of cognitive functioning have been identified through a latent profile analysis in a cohort of 1212 MS patients: preserved cognition, mild verbal memory/semantic fluency involvement, mild multidomain involvement, severe executive/attention involvement, and severe multidomain impairment (Fig. 8).

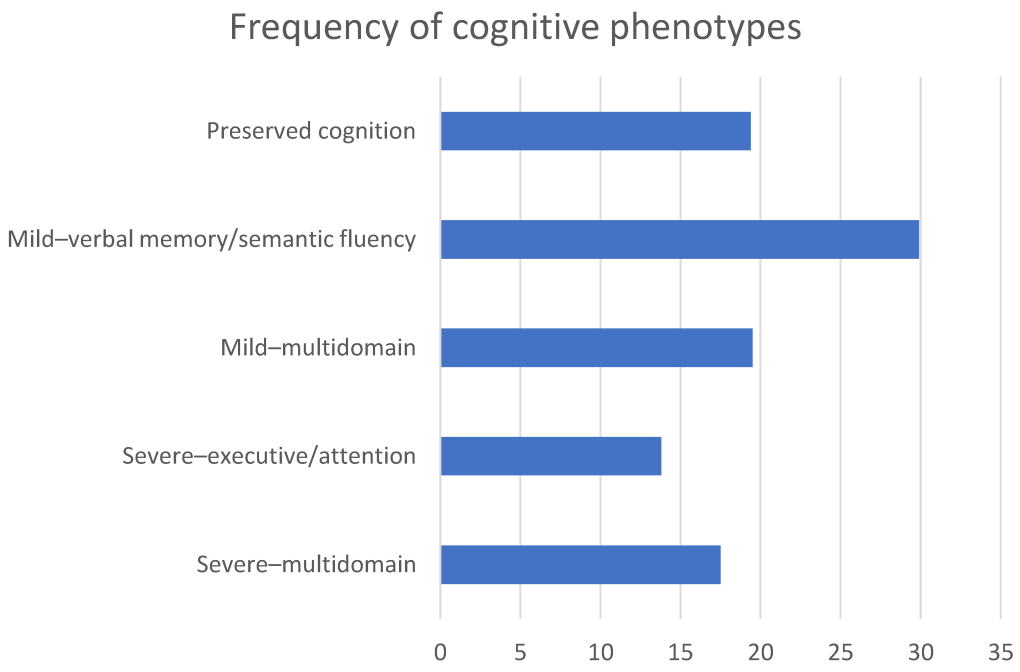

Fig. 8 - Percentage of different cognitive phenotypes in multiple sclerosis patients

In addition to the cognitive domains previously discussed, MS can affect various other cognitive functions and processes. Recent studies have highlighted differential impairments in fundamental aspects of social cognitive processing among MS patients. Furthermore, disturbances in learning and memory processes, coupled with typical dysfunctional behaviors like deficits in action control and motor inhibition, have been identified as central factors in various neurodegenerative disorders.

Additionally, less explored aspects such as altered emotion perception may also contribute to cognitive dysfunction in MS[139].

AIM OF THE STUDY

The analysis of demyelinating lesions distribution and pattern on brain and spinal MRI in patients with MOGAD has been extensively explored in recent years through cohort studies, documenting various distinctive aspects of this disease compared to MS or NMOSD-AQP4, as previously described. However, data on presence of brain atrophy in MOGAD patients, including both total brain volume and the distribution between WM and GM – as well as the presence of regional atrophy -, remains scarce. Only recently some studies have highlighted specific regions of increased GM atrophy in MOGAD compared to HC; however, longitudinal assessments of global brain atrophy in these patients are still limited in the literature, specifically in adult patients.

Furthermore, there is currently no systematic assessment of CI in patients with MOGAD, nor comparisons with other demyelinating diseases.

The primary endpoint of this multicenter study, based on longitudinal analysis of two MRI scans performed at two different time points, is to compare the degree of global brain atrophy, expressed as percentage brain volume change (PBVC), in two matched cohorts of patients affected by MOGAD or MS and in a group of HC.

Secondary objectives of the study include:

1. A cross-sectional analysis of brain lesions distribution and pattern in MOGAD and MS patients
2. A cross-sectional comparison of baseline values of global brain, WM and GM volumes between the two cohorts
3. A cross-sectional comparison of regional brain volumes in the two groups, including cerebrum, cerebellum, thalamus, putamen, caudate, and hippocampus
4. A cross-sectional comparison of differences in T2 lesion load between the two groups; additionally, a longitudinal assessment of T2 lesion load progression between the two cohorts
5. A descriptive analysis of cognitive profile of MOGAD and MS cohorts.

MATERIALS AND METHODS

1. STUDY POPULATION

This longitudinal multicenter observational study involves 18 centres in Italy, many of which are part of the "Raising Italian Researchers in Multiple Sclerosis" (RIREMS) group. MOGAD patients are prospectively recruited at each participating centre. Enrolment started on 31/01/2017 and will end on 31/12/2025. This study has been approved by the ethics committee for clinical research of Verona and Rovigo provinces, Italy (n. 1052CESC). Eligible cases are recruited according to the following inclusion criteria: patients ≥18-years-old of both sexes; signed written informed consent; at least one clinical episode compatible with IDE of the CNS; MOG-IgG positivity on serum and/or CSF sample (the latter with associated clinical and MRI features clearly suggestive for MOGAD); clinical follow-up of at least six months. After enrolment, a screening assessing the quality of baseline brain MRI scan has been performed by an investigator at Verona MS Center to evaluate if all scans could undergo processing with dedicated software. Patients whose MRI scans did not qualify for further analysis have been excluded from the study.

MS patients are recruited at each participating centre or at Verona MS centre according to the following inclusion criteria: patients ≥18 years-old, age (±5 years) and sex-matched to MOGAD cases; MS diagnosis according to 2017 McDonald Criteria; signed written informed consent.

For the longitudinal and cross-sectional analysis of PBVC, global brain, WM and GM volumes, a comparison of MOGAD and MS patients with a group of age- and sex-matched control subjects (all Caucasians) have been performed, using brain MRI scans performed 2 years apart available from an online repository ("Wayne State Study 11 Dataset, available at http://fcon_1000.projects.nitrc.org/indi/retro/wayne_11.html).

2. STUDY DESIGN

After signing written informed consent, patients enter the study at baseline (T0), where demographic and clinical variables are assessed. A neuropsychological assessment is also performed, as well as a brain MRI scan (±3 months from baseline) and serum MOG-IgG test. At T1 evaluation, which follows the baseline visit after 12±6

months, a clinical assessment is performed, as well as a new brain MRI and a serum MOG-IgG test for MOGAD patient. Each patient undergoes a longitudinal and cross-sectional (at baseline) evaluation of brain MRI images through dedicated software (Fig. 9).

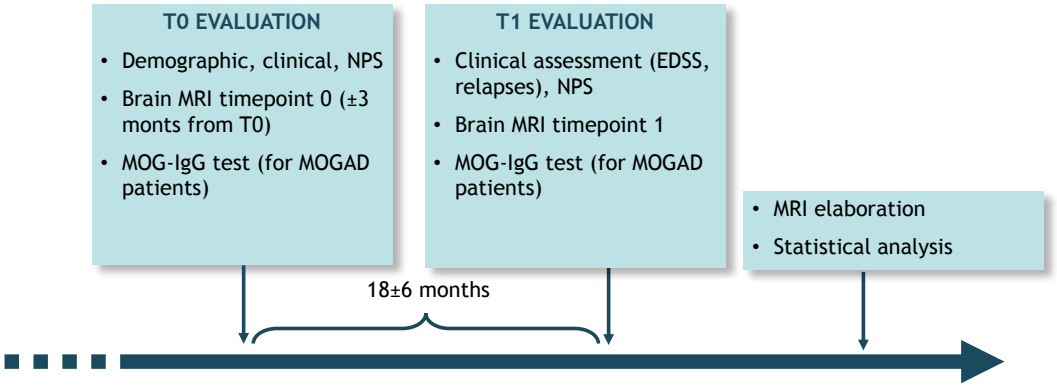

Fig. 9 - Study design

3. CLINICAL ASSESSMENT

The clinical variables collected at baseline and at T1 include: demographic data, onset date of the IDE, anatomical area involved at onset and associated symptoms, disease duration at T0 (expressed as the difference in months between date at onset and date at T0 MRI scan), EDSS scores at baseline and follow-up MRI, previous relapses before the first MRI and during the follow-up period, time interval between the first and second MRI scans, use of disease-modifying drugs (DMDs) during follow-up, neurological examination with assessment of EDSS score and its functional systems (FS) at the first and second MRI. Furthermore, the study includes the date of lumbar puncture, standard examination characteristics, increase in IgG index, and presence of OCBs.

4. MRI PROTOCOL

MRI scans are acquired at each participating centre using the same MRI protocol and scanner for both timepoints. T1-weighted 3D scans are used for the estimation of PBVC and for the cross-sectional assessment of whole brain, GM, WM and regional brain. The machines used are Philips Ingenia 1.5 Tesla, Philips Achieva 1.5 Tesla

(Philips, Eindhoven, Netherlands), and Siemens Avanto 1.5 Tesla (Siemens AG, Berlin, Germany).

3D FLAIR scans are used for T2 lesion distribution and volume assessment. Double inversion recovery (DIR) 3D sequences are used for the assessment of cortical lesions, whenever available (for 5 MOGAD and 5 RRMS cases this sequence has not been acquired in the study protocol). The evaluation of number, distribution and characteristics of brain lesions at baseline is performed visually at each participating center by the local investigator, according to a pre-specified data log made available to the centers at study start.

The MRI sequence protocol exhibits the following characteristics:

1. T1-3D Turbo Field Echo – TR 7,6 ms, TE 3,6 ms, 1.10 mm thickness, matrix 512 x 512, 150 slices or
2. T1 3D MP-RAGE: TR 1880 ms, TE 3,9 ms, 1.25 mm thickness, matrix 512 x 512, 144 slices;
3. FLAIR 3D: TR 4800 ms, TI 1660 ms, TE 306 ms, 0.57 mm thickness, matrix 256 x 256, 321 slices;
4. DIR 3D – TR 5500 ms, TI 2510 ms, TE 334 ms, voxel 0.98 x 0.98, 0.68 mm thickness, matrix 256 x 256, 264 slices.

Annualized whole brain volume changes between baseline and T1 – expressed as PBVC/y – are assessed using SIENA software[140], part of the FMRIB Software Library (FSL – www.fmrib.ox.ac.uk/fsl/). This registration-based method uses images from two timepoints to assess brain volume changes by giving an estimate of percentage brain volume change (PBVC) between the 2 scans. Through a series of FSL programs, SIENA removes non-brain tissue from the two images, co-registers them, and analyzes PBVC. During the analysis, an automated procedure for brain tissue extraction can be utilized to achieve more precise removal of the eyeballs and other non-brain tissues, aiming to obtain a more accurate estimate of brain atrophy (Fig. 10).

Normalized brain volume (NBV), white matter (WM) and grey matter (GM) volume at baseline are assessed using SIENAX software[141], part of the same FMRIB suite described earlier. SIENAX measures the volume of the brain from a single MRI scan and then normalizes it to a standard skull to yield NBV. NBV can be thought of as the fraction of the skull that is filled with brain. It also provides normalized white and gray matter volumes values.

Regional volumes are measured using VolBrain, an automated open-source software recently published. It uses anonymized T1-weighted 3D images in .nifti format for elaboration and generates a report with volumes of major intracranial tissues[142].

T2-lesions volume (T2LV) is assessed for each timepoint using ITK-SNAP[143] (http://www.itksnap.org/pmwiki/pmwiki.php), a semi-automated software that allows lesion segmentation on FLAIR-3D sequences. The T2 lesion mask automatically generated through ITK-SNAP Is then visually inspected and manually corrected when necessary by an investigator from Verona MS Center.

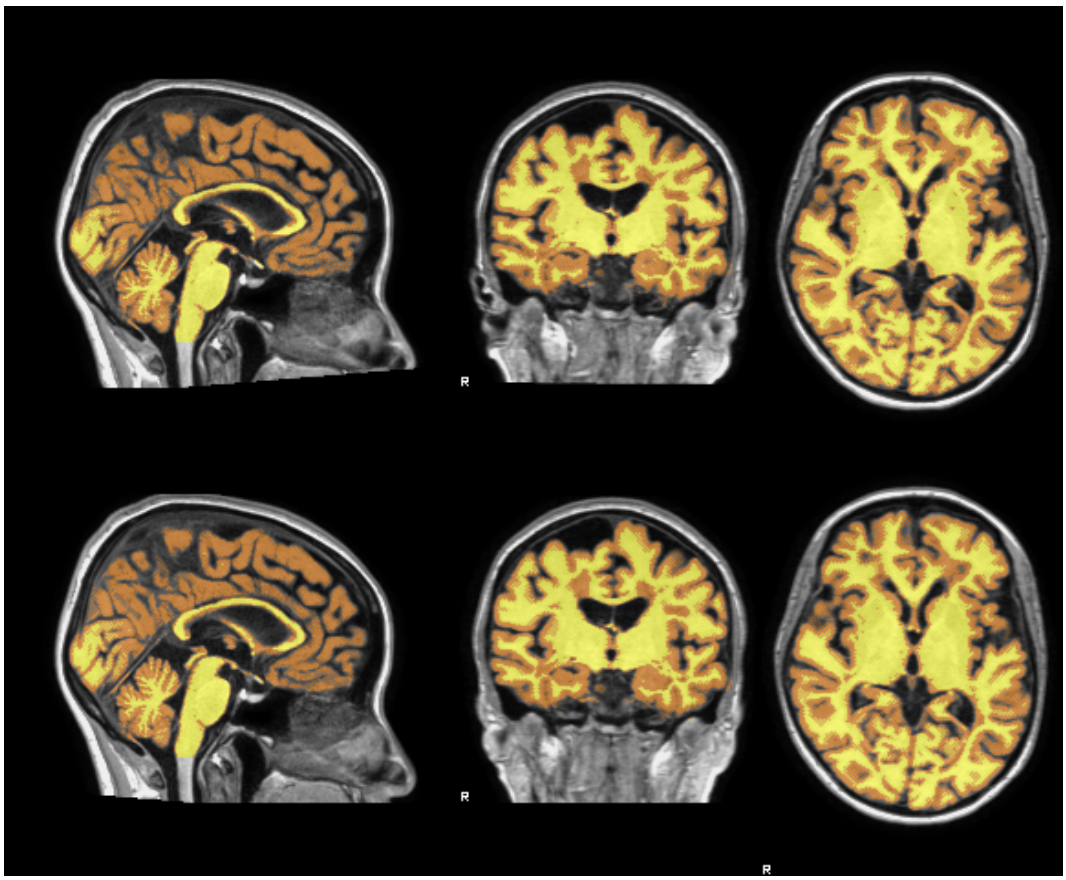

Fig. 10 - Example of extraction and comparison of brain volumes at two timepoints using T1 3D sequences in SIENA

5. MOG-IgG ASSAY

The measurement of serum or CSF MOG-IgG antibody titre has been performed at the Neuropathology Laboratory of the University of Verona using an

immunofluorescence technique on cell-based assays (CBA) with recombinant HEK293A cells transfected with full-length MOG antigen in its conformational form, following a well-described protocol as previously detailed[44,47]. In summary, the procedure involves the following steps:

1. Blocking of antigens with goat IgG (Sigma-Aldrich) for 10 minutes in phosphate-buffered saline (PBS)/10% fetal calf serum (FCS) (both from Sigma-Aldrich).
2. Incubation of cells with patient serum samples diluted 1:20 and 1:40 in PBS/10% FCS for 1 hour at 4°C.
3. After 3 washes with PBS/10% FCS, cells are incubated for 30 minutes at room temperature with CyTm 3-conjugated goat anti-human IgG (H+L, Jackson ImmunoResearch Laboratory, West Grove, PA, USA; diluted 1:200 in PBS/10% FCS).
4. Cells are washed twice and stained with DAPI (Sigma-Aldrich, diluted 1:10,000 in PBS/10% FCS) to exclude dead cells.
5. The prepared slides are immediately analysed using a fluorescence microscope (Zeis, Axio Vert.A1).

Serum samples are tested at dilutions of 1:20 and 1:40; positivity for MOG-IgG is titrated using serial dilutions, setting the positivity threshold at 1:160, as previously defined[47]. CSF is tested undiluted and at 1:2 dilution, with subsequent serial titrations[50].

6. NEUROPSYCHOLOGICAL EVALUATION

Participants were informed about the procedure of the task and were made aware of their right to withdraw from the assessment at any time. The experiment was conducted in accordance with the ethical guidelines established by the University of Verona.

For the cognitive assessment of the subjects, the BICAMS battery was used. It was designed as a tool for basic cognitive screening aimed at investigating the presence of cognitive deficits in people with MS[144]. Particularly, BICAMS was introduced based on a literature review by an international group of experts who selected tests based on their psychometric properties and ease of use in clinical practice[145]. Patients with multiple sclerosis (MS) can complete the test in 15-20 minutes using only a pencil, paper sheets, and a timer. The test evaluates the key domains affected in MS. Normative values for the Italian version of the battery have been available since 2014.

The BICAMS battery consists of:

1. *Symbol Digit Modalities Test* (SDMT)[146]: it assesses processing speed, working memory, and attention in visual scanning. It consists of pairs of a digit associated with a symbol, arranged in rows where nine symbols appear randomly. The patient must state the number corresponding to each symbol. The test duration is 90 seconds.
2. *California Verbal Learning Test* (CVLT-II). This test assesses verbal memory and consists of a list of 16 words from four different categories, with four words per category presented randomly. The list is read aloud by the examiner five times to the patient in the same order, at a rate of approximately 1 word per second. Patients are required to recall as many words as possible, in any order, after each reading. The test duration is 5-10 minutes.
3. *Brief Visuospatial Memory Test-Revised* (BVMT-R). The test evaluates visual memory and involves a 2x3 matrix of 6 geometric figures. The patient carefully observes the matrix for 10 seconds, after which it is removed, and they are asked to reproduce the figures in the correct shape and position. The test is repeated three times in total.

Since patients with MS often experience fatigue that affects both motor and cognitive functions, in addition to the BICAMS battery, the Fatigue Scale for Motor and Cognitive Functions (FSMC)[147] has been included in the assessment to provide a comprehensive cognitive profile of the subject's current situation. This scale aims to investigate perceived motor and cognitive fatigue. It consists of 20 items, where the subject rates each item from "never" to "always". The level of fatigue (none, mild, moderate, severe) is assigned based on the score of each scale (cognitive, motor, total), obtained by summing the frequency values assigned by the subject to each item.

Furthermore, mood state is acknowledged to affect concentration, learning ability, and can influence fatigue levels; hence, the Beck's Depression Inventory Scale (BDI-II)[148] has been included in the neuropsychological assessment. This scale comprises 21 statements to assess the presence of depressive symptoms. The subject selects the statement that best matches with their mood state over the past two weeks for each item. The final score is the sum of the values assigned to each statement.

The full booklet of neuropsychological tools administered to patients is available in Appendix 1.

7. STATISTICAL ANALYSIS

Given the lack of literature on expected brain volume change in MOGAD patients, sample size calculation to define significance in annual PBVC differences between MOGAD and MS subjects has been based on studies comparing MS patients with healthy individuals. Specifically, it has been assumed that the expected PBVC value for MOGAD subjects could be comparable to that of RRMS patients (null hypothesis), with an annual percentage change of -0.52±0.29%[127]. Based on this assumption, a sample size of 20 MOGAD patients and 30 MS patients is calculated to achieve 80% statistical power with 95% confidence interval. The target sample size for MOGAD subjects has been increased to 25 to mitigate the impact of potential drop-outs on study power.

Quantitative variables are presented as mean and standard deviation if normally distributed, or as median and range (minimum-maximum) if not. Categorical variables are expressed as absolute and relative frequencies. To assess whether variables included in the statistical analysis are normally distributed, a Kolmogorov-Smirnov test is initially performed, and frequency histograms are visually examined. For normally distributed variables, an independent samples t-test is applied to assess mean differences between MOGAD and MS; comparison between continuous variables between MOGAD, MS and HC is computed by one-way analysis of variance (ANOVA), followed by a post-hoc Tukey's multiple comparison test. Additionally, the chi-square test or Fisher's exact test is employed to evaluate group differences in categorical variable frequencies. Bonferroni correction is applied for repeated measures. Partial correlation has been performed to investigate the relationship between neuropsychological, clinical and MRI continuous variables. A significance level of $\alpha < 0.05$ (two-tailed) is adopted. Statistical analysis is conducted using Jamovi software (Version 2.5; The Jamovi Project, available at https://ww.jamovi.org).

RESULTS

To date, the study has recruited 16 MOGAD adult patients (9 F); the MS cohort consists of 44 patients with RRMS (26F). Brain MRI scans from 14 control subjects age- and sex matched have also been analysed for comparison with MOGAD and MS patients Fig. 11.

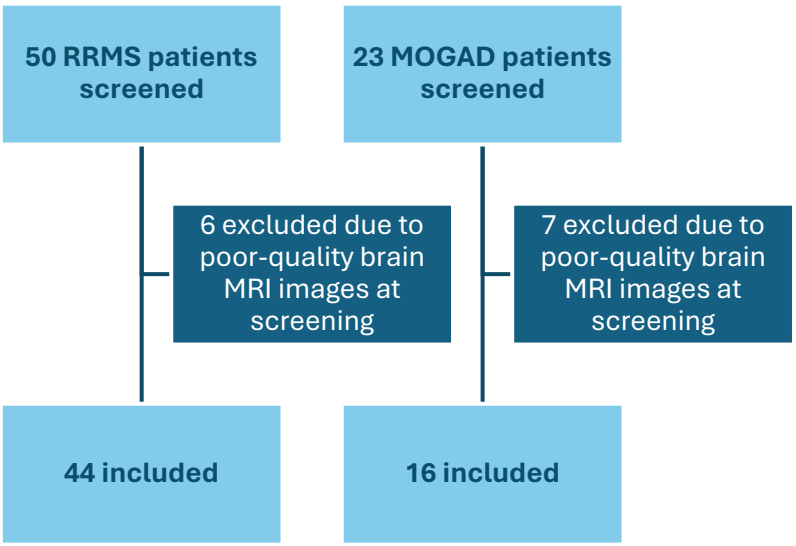

Fig. 11 – Study Flow-chart

1. BASELINE CLINICAL AND MRI ASSESSMENT

Demographic, clinical and paraclinical characteristics of MOGAD, MS and HC subjects are summarized in Table 1.

Median age at baseline is 36 years in all groups (range 23-69 for MOGAD, 23-69 years for MS patients and 21-71 for HC, p = 0.935). Median age at disease onset is similar in MOGAD (33 years, range 21-68) and MS patients (31 years, range 16-47, p = 0.482).

Sex ratio is equally distributed in the two patient cohorts and in HC (56.2% of females with MOGAD, 59.1% with MS and 64.2% in HC group, p = 0.902), Fig. 12. Female to male ratio in MOGAD group is 1.29:1.

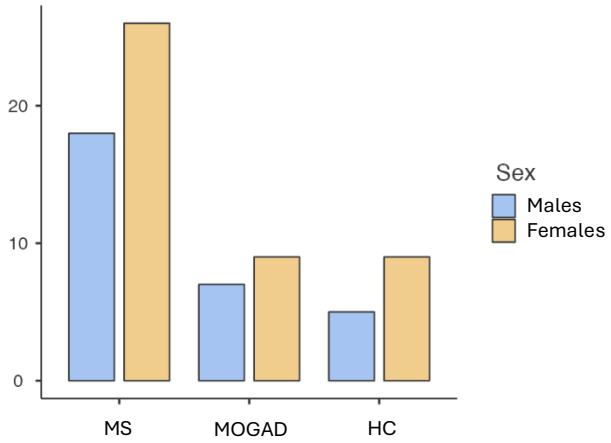

Fig. 12 - Sex distribution in the study cohorts

At onset, the involved anatomical area is optic neuritis in 37% of MOGAD and in 14% of MS patients, myelitis in 31% and 56%, brainstem syndrome in 13% and 19%, encephalopathy in 6 and 9% and multifocal in 13% and 2% respectively (Fig. 13). No significant differences have been observed in the distribution of the involved anatomical areas at onset between the two groups according to chi-squared test and Bonferroni correction.

Table 1 - Demographic, clinical and MRI features of MOGAD, MS cases and HC

	MOGAD (n = 16)	**MS (n = 44)**	**HC (n = 14)**	**p value**
Median age at T0– years (range)	36 (21-69)	36 (23-69)	36 (21-71)	0.935
Median age at onset – years (range)	33 (21-68)	31 (16-47)		0.482
Sex – n (%)				0.902
F	9 (56.2)	26 (59.1)	9 (64.2)	
M	7 (43.8)	18 (40.9)	5 (35.8)	
Clinical onset – n (%)				0.167
Optic neuritis	6 (37.5)	6 (13.6)		
Monolat.	7 (43.8)	5 (11.4)		
Bilat.	0 (0.0)	1 (2.3)		
Myelitis	5 (31.8)	24 (54.5)		
Brainstem	2 (12.5)	9 (20.5)		
Encephalopathy	1 (6.3)	4 (9.1)		
Multifocal	2 (12.5)	1 (2.3)		
MOGAD clinical course – n (%)				
Monophasic	11 (68.8)			
Relapsing	5 (31.2)			
Disease duration at T0 – median months (range)	8 (0-65)	60 (0-418)		**<0.001**
EDSS – median (range)				
T0	2.0 (0-6)	1.5 (0-4.5)		0.793
T1	0.0 (0-5.5)	1.5 (0-4.0)		0.050
Previous relapses – median (range)	0 (0-3)	1 (0-12)		**0.008**
Relapsed patients during follow-up – n (%)	2 (33.3%)	8 (18.2%)		0.384
Interval between MRI scans – months (range)	12 (12-17)	13 (12-18)	24 (24)	0.595
Ongoing DMD at T0 – n (%)				**0.037**
No DMD	9 (56.3)	12 (27.3)		
Under DMD	7 (43.7)	32 (72.7)		
Brain MRI lesions at T0 – n of patients (%)				
Cortical				**0.007**
0	11 (68.8)	16 (36.3)		
1-2	0 (0.0)	9 (20.5)		
≥ 3	0 (0.0)	14 (31.8)		
DIR not acquired	5 (31.2)	5 (11.4)		
Juxtacortical				**< 0.001**
0	10 (62.4)	5 (11.4)		
1-2	3 (18.8)	4 (9.1)		
≥ 3	3 (18.8)	35 (79.5)		
Periventricular				**< 0.001**
0	8 (50.0)	1 (2.3)		
1-2	6 (37.6)	2 (4.6)		
≥ 3	2 (12.4)	41 (93.1)		
Thalamus				0.141
0	16 (100.0)	32 (72.7)		
1-2	0 (0.00)	10 (22.7)		
≥ 3	0 (0.00)	2 (4.6)		
Corpus callosum				**<0.001**

0	16 (100.0)	16 (36.4)		
1-2	0 (0.0)	16 (36.4)		
≥ 3	0 (0.0)	12 (27.2)		
Basal ganglia				0.415
0	15 (93.8)	35 (79.5)		
1-2	1 (6.2)	9 (20.5)		
≥3	0 (0.0)	0 (0.0)		
Brainstem				**0.001**
0	13 (81.3)	11 (25.0)		
1-2	3 (18.7)	29 (69.9)		
≥ 3	0 (0.0)	4 (9.1)		
Cerebellar				0.127
0	14 (87.5)	24 (54.5)		
1-2	2 (12.5)	18 (40.9)		
≥ 3	0 (0.0)	2 (4.6)		
Tumefactive lesions				**0.024**
0	13 (81.2)	43 (97.7)		
≥1	3 (18.8)	1 (2.3)		
Blurred margins				**0.020**
0	12 (75.0)	42 (95.5)		
≥1	4 (25.0)	2 (4.5)		
Contrast enhancement				0.329
0	13 (81.0)	26 (59.2)		
≥1	2 (12.5)	6 (13.5)		
n.a.	1 (6.5)	12 (27.3)		
New T2-lesions				0.178
0	14 (87.5)	31 (70.5)		
≥1	2 (12.5)	13 (29.5)		
Neuropsychological assessment – median (range)	**MOGAD (n = 9,** 6F**)**	**MS (n = 19,** 11F**)**		
SDMT	54.6 (34.8-59.0)	50.0 (35.1-61.9)		0.557
CVLT-II	55.1 (37.9-72.7)	52.7 (35.8-68.3)		0.735
BVMT-R	49.1 (30.4-63.0)	48.3 (37.2-65.5)		0.849
BDI-II	3 (1-17)	8 (1-14)		**0.035**
FSMC				
Cognitive	20 (11-39)	23 (13-44)		0.136
Motor	24 (10-38)	26 (16-43)		0.276
Total	42 (25-77)	51 (29-87)		0.184

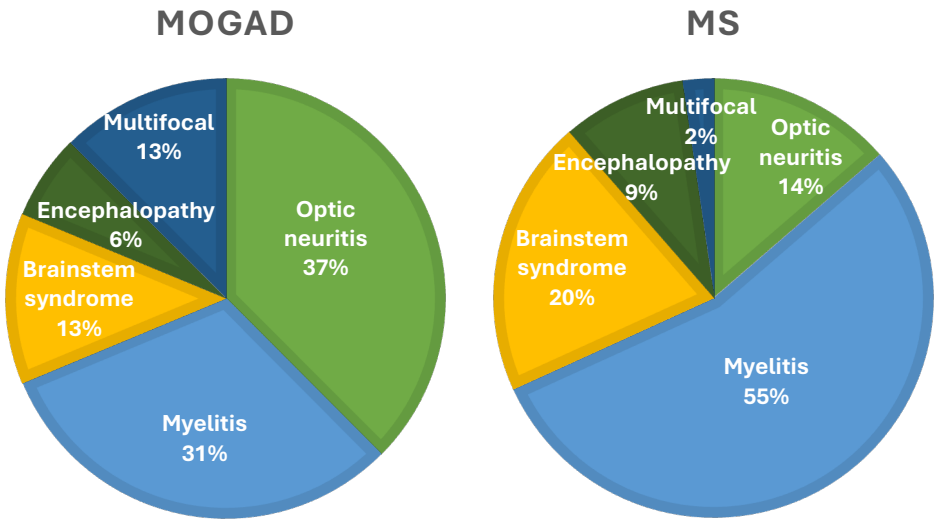

Fig. 13 - Involved anatomical area at disease onset in MOGAD and MS patients

Median EDSS at baseline was 2.0 (range 0-6) for MOGAD and 1.5 (0-4.5) for MS group (p = 0.793); at T1, it was 0.0 (range 0-5.5) for MOGAD and 1.5 (range 0-4.0) for MS cohort, with a difference showing a trend towards significance (Fig. 14).

Interval between T0 and T1 is similar between the groups, being 12 months (range 11-17) for MOGAD and 13 months (range 11-18) for MS patients (p = 0.595). Conversely, median disease duration from onset to baseline is significantly higher in MS group (126 months, range 33-497) compared to MOGAD patients (69 months – range 22-115, p < 0.001).

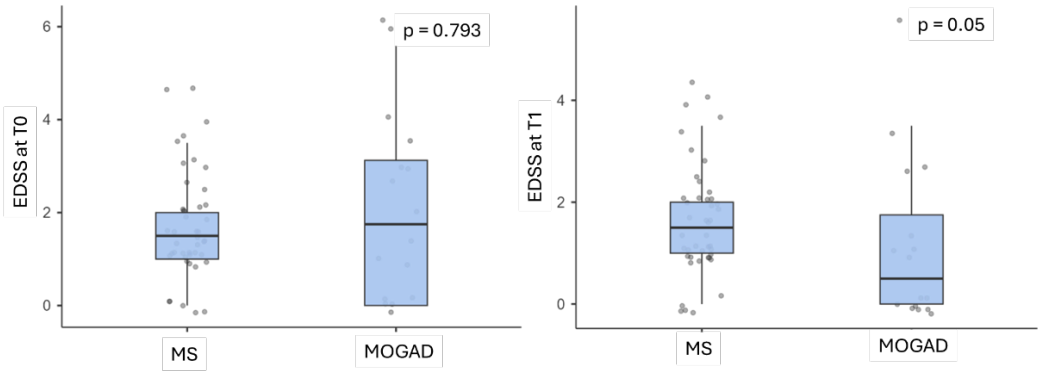

Fig. 14 - Median EDSS in MOGAD and MS cohort at T0 and T1. Horizontal black bars represent median values, squares are means.

Median number of relapses before T0 is significantly lower in MOGAD (0, range 0-3) compared to MS patients (1, range 0-12, p = 0.008). 2 MOGAD patients have experienced a relapse during the study follow-up, with symptoms compatible with

myelitis, compared to 8 MS cases. Overall, 5 MOGAD patients (33.3%) show a relapsing phenotype, while for 11 of them the disease is monophasic.

The distribution and number of brain lesions for the two groups are summarized in Fig. 15. Overall, the number of lesions is significantly reduced in MOGAD patients compared to those with MS for almost all considered locations. Specifically, 8 MOGAD patients (50%) show no brain lesions. MOGAD subjects have fewer cortical lesions ($p = 0.002$), absence of periventricular, juxtacortical, and corpus callosum lesions ($p = 0.001$), as well as brainstem lesions ($p = 0.004$). Conversely, MOGAD patients exhibit a significantly higher number of tumefactive lesions ($p = 0.024$) and lesions with blurred margins ($p = 0.020$). No statistical difference has been observed between the two cohorts in the proportion of patients with at least one new T2 lesion at T1 MRI.

For the evaluation of the neuropsychological features of patients with MOGAD and MS, see page 48.

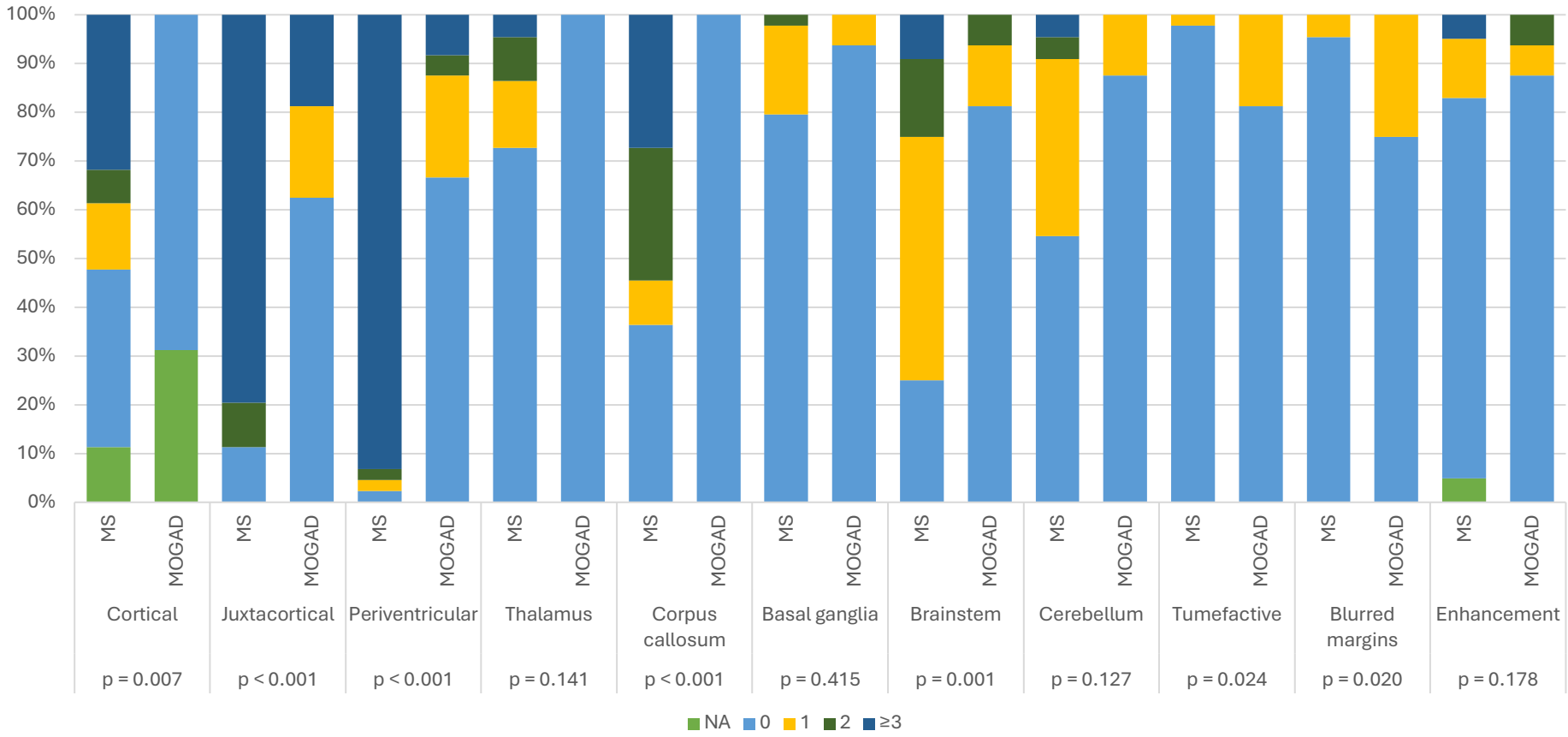

Fig. 15 - Percentage of MOGAD or MS patients with 0, 1, 2, or ≥3 lesion in different brain areas

2. BRAIN VOLUME MEASURES

Mean PBVC/y is significantly different among MOGAD (-0.143±0.366%), MS patients (-0.502±0.444) and HC (-0.07±0.425%, p = 0.002); post-Hoc analysis with Tukey test shows significantly higher mean PBVC in MS compared to MOGAD patients (mean difference -0.359, p = 0.014) and to HC (mean difference -0.428, p = 0.005) (Fig. 16).

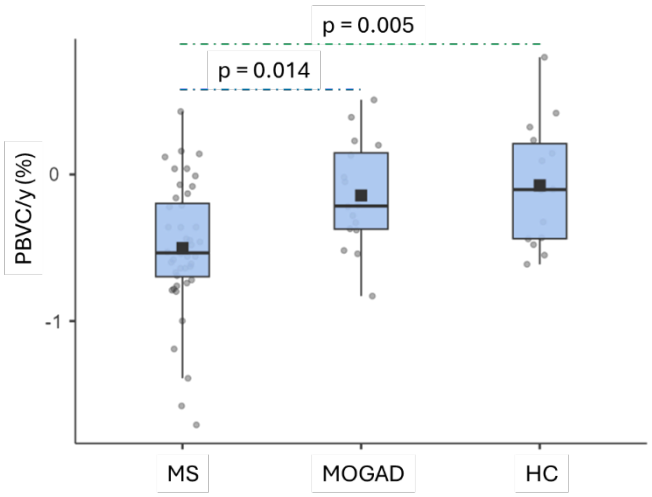

Fig. 16 – Annualized percentage brain volume change in MS, MOGAD and HC. Horizontal black bars represent median values, squares are means.

Cross-sectional analysis performed with SIENAX shows that mean NBV is significantly different among MS (1478,37±99.95 cm^3) MOGAD (1560.1±93.96 cm^3) and HC (1549.75±80.58 cm^3, p 0.007). In particular, post-Hoc analysis reveals a significant difference between MS and MOGAD cohorts (mean difference -81.73 cm^3, p = 0.012) and a borderline significant difference between MS and HC groups (mean difference -71.4 cm^3, p = 0.045) (Fig. 17).

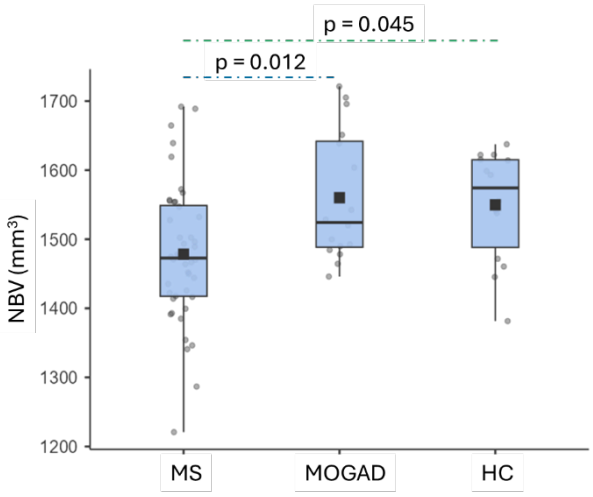

Fig. 17 – NBV distribution in MS, MOGAD and HC. Horizontal black bars represent median values, squares are means.

Mean GM volume does not differ among the groups (data not shown). Conversely, mean WM volume is significantly different between MS (714.16±57.75 cm^3), MOGAD cases (757.72±61.71 cm^3) and HC (755.99±36.98 cm^3, p = 0.006). Post-hoc analysis shows a significant difference between MS and MOGAD cases (mean difference -43.6 cm^3, p = 0.024) and a borderline significant difference between MS and HC cohorts (mean difference -41.83 cm^3, p = 0.043) (Fig. 18).

No significant differences are observed for median regional volumes of cerebellum, thalamus, caudate, putamen and hippocampus (data not shown).

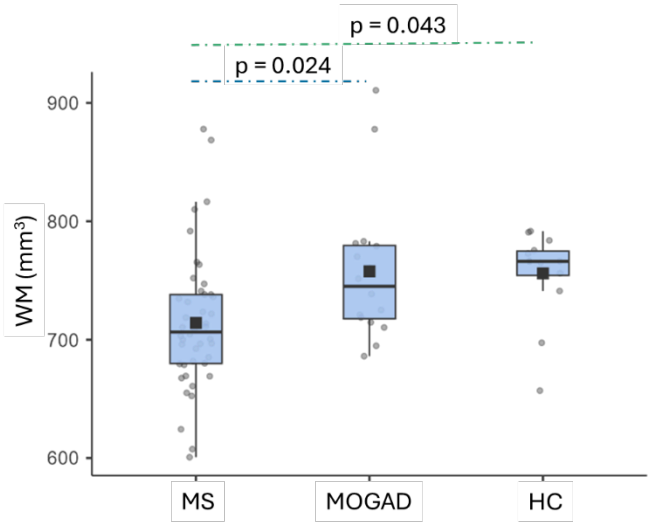

Fig. 18 – WM volume distribution in MS, MOGAD and HC. Horizontal black bars represent median values, squares are means.

At baseline, median T2-lesion volume is significantly higher in MS (4.46 cm^3, range 0.31-94.3) compared to MOGAD patients (0.14 cm^3, range 0-105) (Fig. 19). Median T2-lesion volume increases from T0 (4.46 cm^3, range 0.31-94.3) to T1 (4.96 cm^3, range 0.3-95.1, p < 0.001) in MS cases, but not in MOGAD (T0: 0.14 cm^3, range 0-105; T1: 0.125 cm^3, range 0-105, p = 0.262) (Fig. 20).

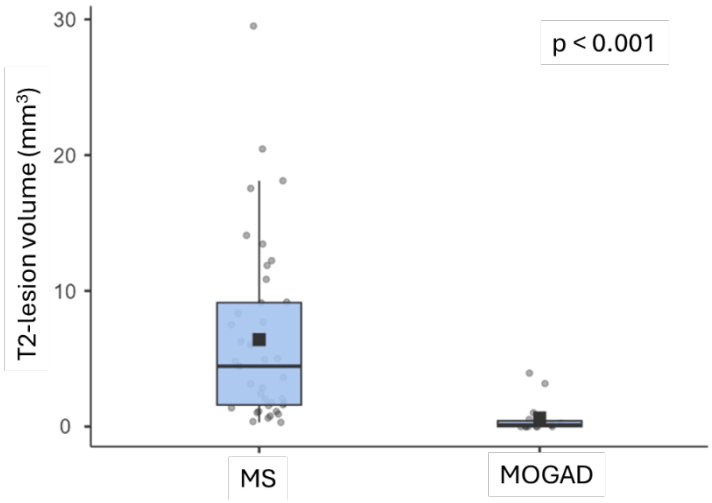

Fig. 19 – T2-lesion volume at T0. Horizontal black bars represent median values, squares are means.

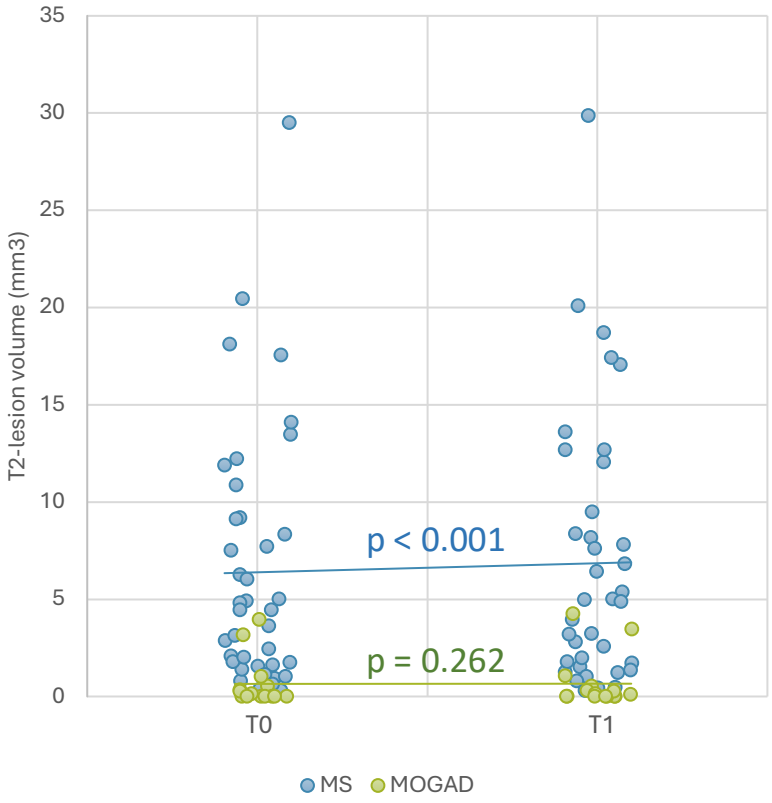

Fig. 20 – T2-lesion volume distribution at T0 and T1 in MOGAD and MS patients.

3. NEUROPSYCHOLOGICAL ASSESSMENT

To date, 8 MOGAD (6F) and 19 MS (11F) patients have completed the neuropsychological (NPS) assessment. Mean disease duration is 70±28 months in MOGAD and 102±50 months in MS patients (p = 0.088). Median age at T0 is 37 years (range 23-69) in MOGAD and 34 years (23-58) in MS cases (p = 0,236). Overall, NPS performances are comparable between MOGAD and MS patients. At baseline, median scores of the neuropsychological tests do not significantly differ. Conversely, BDI-II median score is significantly higher in MS (8 – range 1-14) compared to MOGAD group (3 – range 1-17, p = 0.035) (***Table 1***, Fig. 21). Fatigue – both cognitive and motor – is similar across the cohorts. However, MOGAD patients report that their concentration and learning abilities have not changed after diagnosis. Beyond the cognitive sphere, the disease in this group does not seem to have negatively impacted the perception of motor fatigue, which remains unchanged or slightly increased since the diagnosis. Only one MS and one MOGAD patient have a corrected SDMT score below norms both at T0 and at T1 evaluation. Compared to T0, NPS performances at T1 have not significantly changed in both groups. Within MS and MOGAD cohorts, no significant correlations have been observed between corrected scores of NPS tests at T0, brain volumes and T2-lesion volume (data not shown).

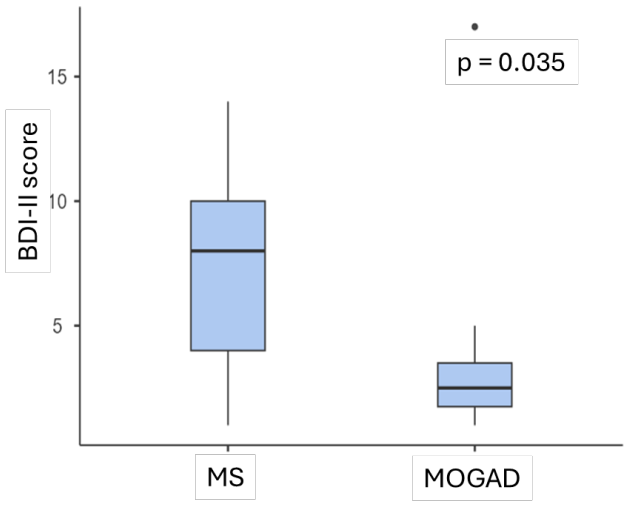

Fig. 21 - BDI-II score at baseline in MOGAD and MS patients. Horizontal black bars represent median values, squares are means.

DISCUSSION

The present study evaluated the brain volumetric characteristics of subjects with MOGAD compared to patients with MS, using both cross-sectional and longitudinal designs.

1. CLINICAL FEATURES OF MOGAD COHORT

In the present study, MOGAD cases show overall clinical features in line with previous reports, with an almost equal distribution among genders and a low predominance of females compared to NMOSD-AQP4 and MS[40,149]. We also confirm that optic nerve and spinal cord are the preferential anatomical sites clinically involved in adults with MOGAD at onset and during follow-up[14]. Simultaneous involvement of the optic nerve and spinal cord is rare in our MOGAD cohort, in which none of the patients has experienced area postrema syndrome, contrasting with NMOSD-AQP4. Our data also provide evidence that MOG-Ab-associated conditions are generally less severe than AQP4-Ab-related ones in terms of attack severity, disease course, and final outcome.

The percentage of patients who presented with an onset of cerebral syndrome, ADEM-like or multifocal, is consistent with the available literature[40]. One third of patients show a relapsing disease course, which is in line with previous evidence from the literature[40].

2. LONGITUDINAL ANALYSIS OF BRAIN VOLUMES

In our study, mean PBVC/y is different between MOGAD, MS and HC and, particularly, is significantly lower in MOGAD compared to MS patients. Mean PBVC/y observed in the MS group is similar to the estimates available from previous studies[126,127]. There is very little data about mean PBVC/y in MOGAD patients. In particular, a recent study on 8 MOGAD, 22 NMOSD-AQP and 34 MS patients showed a reduction of whole brain and cortical gray matter volumes that was not different among the groups, although lacking a group of control subjects[150]. In our study, mean PBVC/y of MOGAD patients was similar to the value estimated for the general population[151], and to the estimate

of PBVC of our control group. Conversely, MS subjects showed a significantly higher PBVC/y compared to controls. Hence, it might be suggested that brain volume loss could be lower, if not absent, in MOGAD patients. A recent study has accordingly shown a significantly lower PBVC/y in NMOSD-AQP4 compared to MS patients[152], thus suggesting, together with our findings, that brain atrophy might be related to neuropathological mechanisms that are exclusive of MS. The contrasting evidence of our study compared other already published could be due to the small sample sizes, thus needing further ascertainment in bigger cohorts.

We showed that T2-lesion load was almost stable over time in MOGAD patients for both volume and number of lesions, while it increased in the MS cohort. This finding is in line with a study on MOGAD patients, in which MOG-IgG positive patients initially diagnosed with MS did not show the typical "silent increase" in lesion volume[26]. Moreover, the increase in T2 lesion volume has been proposed as a red flag for the diagnosis of MOGAD[61]. A recent study[153] showed that only 3% of stable MOGAD patients underwent a silent T2 lesion increase, which is in contrast with the robust evidence of the appearance of new asymptomatic lesions in MS patients[86].

Our study suggests that, unlike MS patients, MOGAD subjects are probably not affected by brain atrophy, and do not show a significant increase in T2 lesion volume over time. These findings could be related to different neuropathological substrates in the two diseases, with a discrete inflammatory activity in MOGAD patients that, once exhausted, does not switch towards an intrathecal chronic inflammation, which is instead the basis of the neurodegenerative processes in MS[82]. Accordingly, a study on the CSF features of MOGAD cases has shown that the most relevant alterations in terms of blood-brain barrier damage, increased cellularity and CSF proteins are mainly related to the acute attack, and tend to recover in the remission phases[52(p1)]. Moreover, it has been recently shown that serum neurofilament light chain levels are increased at MOGAD onset, while they tend to decrease over time in most patients[149]. A study on 2 autoptic cases and 22 brain biopsies of MOGAD patients has revealed that demyelinating lesions lack the accumulation of activated microglia at lesion border, which typically occurs in slowly expanding or smoldering white matter MS lesions, thus suggesting the absence of a neuropathological mechanism linked to chronic active inflammation in MS[22].

3. BRAIN MRI LESIONS DISTRIBUTION

We showed a clear distinction between MOGAD and MS patients in the distribution, appearance and volume of T2 lesions. In particular, we observed no brain lesions in 50% of MOGAD patients, as previously described by other studies in which up to 50% MOGAD patients show normal brain MRI[154,155]. We also confirmed the clear association of cortico-juxtacortical and periventricular lesions with MS, together with the presence of callosal and periventricular signal abnormalities known as Dawson fingers[156]. We observed that MOGAD patients had a significantly lower lesion load compared with the MS cohort, and that brain lesions appeared tumefactive and with blurred margins in MOGAD, while in MS they had an ovoid shape and clearly demarcated borders. These findings are in line with a previous study which showed that the presence of at least one periventricular/inferior temporal lesion, U-fiber lesion or Dawson-finger lesion can differentiate MOGAD from MS with 90% sensitivity and 95% specificity[157].

4. CROSS-SECTIONAL ANALYSIS OF BRAIN VOLUMES

Mean whole brain volume and WM volume at T0 were significantly higher in MOGAD than in MS patients; conversely, there was no significant difference between HC and MOGAD or MS patients. The role of brain atrophy in MOGAD is still uncertain, and findings from previous studies are discordant. Two studies that compared MOGAD with NMOSD-APQ4 patients and healthy controls did not find a significant difference in whole brain volume between MOGAD cases and controls[113,158]. On the contrary, two other studies showed reduced whole brain volumes in MOGAD compared to controls[111,150]. The reported inconsistencies may be due to the relatively small sample sizes and to the different MRI protocols and software used for brain MRI analysis in each of the studies.

There is more consensus regarding a higher WM volume in MOGAD compared to MS patients[111,113,150], as confirmed by our findings. The higher WM volume in MOGAD patients could be also due to a significantly lower T2-lesion volume, with less inflammatory and neurodegenerative effects in this context.

We did not find significant differences in GM volume between MOGAD, MS patients and HC. This finding is in line with previous data in which GM volume does not differ

between MOGAD patients and HC[158], and with the fact that GM atrophy is known to mainly affect MS patients[159]. However, a study on 20 MOGAD adult patients showed a significantly reduced deep grey matter volume compared to HC, which correlated with lesional volume[114]. Moreover, Fadda et al. observed a delayed age-expected and sex-expected growth of deep grey matter structures – including thalamus, caudate, and globus pallidus – compared to HC[160]. In our study, we did not observe significant differences in deep grey matter volumes in MOGAD compared to MS patients or HC. This could be explained by the relatively small number of cases affected by ADEM or with demyelinating lesions in the deep grey matter structures, possibly lacking the inflammatory mechanisms that could drive the observed volume loss in MOGAD cohorts of the other studies.

5. NEUROPSYCHOLOGICAL ASSESSMENT

In this study, no statistically significant differences in cognitive performances between MOGAD and MS patients have been observed; overall, the two cohorts are characterized by preserved cognitive functions, which do not seem to decline over time. This finding contrasts with the robust evidence of CI involving up to 65% of MS cases during the disease course[139]. This discrepancy could be explained by the small sample size and the relatively short disease duration of both MS and MOGAD cohorts, as well as by the young median age at T0 and by the exclusion of MS patients with a progressive phenotype, which are more prone to develop CI compared to RRMS cases.

This is one of the first studies to investigate longitudinally the cognitive profile of adult MOGAD cases. These patients report that their concentration and learning abilities have not channged after diagnosis. Besides cognitive aspects, this group does not appear to have been negatively affected by the disease in terms of motor fatigue perception, which remains unchanged or slightly worsened after diagnosis. This findings are in line with a study on 29 highly relapsing MOGAD cases, whose clinical outcome was generally favorable, with the exception of two patients who experienced CI[130]. Conversely, Li et al. observed that 4 of 9 MOGAD cases from a retrospective chart review exhibited impaired performances in at least one cognitive domain. However, these patients were mainly affected by encephalitis, in contrast with our cohort in which only 2 patients showed an encephalopathic syndrome at onset.

Hence, our evidence, if confirmed by larger longitudinal studies – possibly with a longer follow-up duration -, could suggest that MOGAD patients that are not affected by encephalitis during the disease course might are unlikely to develop CI.

6. LIMITATIONS

The main limitation of this study is the absence of a shared MRI protocol across all the enrolled subjects, despite the use of the same scanner for T0 and T1 in each patient. However, due to the rarity of MOGAD, we believe that using a multicenter approach to enroll more patients – and to achieve a higher statistical power – could in part counterbalance the technical limitations of using different MRI scanners within each participating center.

Another limitation of our study is the comparison of MOGAD and MS patients with a group of HC obtained from an online repository, although matched for sex, age and ethnicity. However, considering the ethical and organization issues implied in the execution of two MRI exams in healthy people, we believe that the use of brain MRI online repositories might be an acceptable compromise.

Another intrinsic limitation is the different disease duration between the two disease groups, as MOGAD has only recently been considered a specific disease entity. However, limiting the comparison to patients with RRMS disease duration lower than 10 years in a bigger cohort of MOGAD patients could be a possible solution to this issue.

CONCLUSIONS

This study, despite the aforementioned limitations, highlighted the following findings:

- MOGAD patients exhibit significantly different brain volumetric characteristics compared to MS subjects;
- in MOGAD, the degree of global brain and white matter atrophy is lower than in MS subjects;
- lesion burden significantly increases during follow-up in MS patients, while remaining relatively stable in MOGAD subjects;
- Neuropsychological evaluation of MOGAD patients appears to show preserved cognitive profile, at least in patients without encephalopathic involvement during the disease course, with findings that need replication in a larger patient cohort to correlate with MRI data.

Taken together, these findings support the hypothesis that MOGAD represents a distinct entity from MS not only epidemiologically and clinically, but also pathogenetically. Further prospective longitudinal studies are needed to confirm and expand upon the results of this study.

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APPENDIX

1. NEUROPSYCHOLOGICAL ASSESSMENT BOOKLET

BDI-II

Istruzioni. Il presente questionario consiste di 21 gruppi di affermazioni. Per favore legga attentamente le affermazioni di ciascun gruppo. Per ogni gruppo scelga quella che meglio descrive come Lei si è sentito nelle *ultime due settimane* (*incluso oggi*). Faccia una crocetta sul numero corrispondente all'affermazione da Lei scelta. Se più di una affermazione dello stesso gruppo descrive ugualmente bene come Lei si sente, faccia una crocetta sul numero più elevato per quel gruppo. Non scelga più di una affermazione per ciascun gruppo, incluse la domanda 16 ("Sonno") e la domanda 18 ("Appetito"). È importante che non ci sono risposte giuste o sbagliate. Non si soffermi troppo su ogni affermazione: la prima risposta è spesso la più accurata. Grazie.

1. Tristezza
0. Non mi sento triste.
1. Mi sento triste per la maggior parte del tempo
2. Mi sento sempre triste
3. Mi sento così triste o infelice da non poterlo sopportare.

2. Pessimismo
0. Non sono scoraggiato riguardo al mio futuro.
1. Mi sento più scoraggiato riguardo al mio. futuro rispetto al solito..
2. Non mi aspetto nulla di buono per me.
3. Sento che il mio futuro è senza speranza e che continuerà a peggiorare.

3. Fallimento
0. Non mi sento un fallito.
1. Ho fallito più di quanto avrei dovuto.
2. Se ripenso alla mia vita riesco a vedere solo una serie di fallimenti.
3. Ho la sensazione di essere un fallimento totale come persona.

4. Perdita di piacere
0. Traggo lo stesso piacere di sempre dalle cose che faccio.
1. Non traggo più piacere dalle cose come un. tempo.
2. Traggo molto poco piacere dalle cose che di solito mi divertivano.
3. Non riesco a trarre alcun piacere dalle cose che una volta mi piacevano.

5. Senso di colpa
0. Non mi sento particolarmente in colpa.
1. Mi sento in colpa per molte cose che ho fatto o che avrei dovuto fare.
2. Mi sento molto spesso in colpa.
3. Mi sento sempre in colpa.

6. Sentimenti di punizione
0. Non mi sento come se stessi subendo una punizione.
1. Sento che potrei essere punito.
2. Mi aspetto di essere punito.
3. Mi sento come se stessi subendo una punizione.

7. Autostima
0. Considero me stesso come ho sempre fatto
1. Credo meno in me stesso
2. Sono deluso di me stesso.
3. Mi detesto.

8. Autocritica
0. Non mi critico né mi biasimo più del solito. 1. Mi critico più spesso del solito.
2. Mi critico per tutte le mie colpe.
3. Mi biasimo per ogni cosa brutta che mi accade.

9. Suicidio
0. Non ho alcun pensiero suicida
1.Ho pensieri suicidi ma non li realizzerei
2. Sento che starei meglio se morissi.
3. Se mi si presentasse l'occasione, non esiterei ad uccidermi

10. Pianto
0. Non piango più del solito.
1. Piango più del solito.
2. Piango per ogni minima cosa.
3. Ho spesso voglia di piangere ma non ci riesco.

11. Agitazione
0. Non mi sento più agitato o teso del solito.
1. Mi sento più agitato o teso del solito.
2. Sono così nervoso o agitato al punto che mi è difficile rimanere fermo.
3. Sono così nervoso o agitato che devo continuare a muovermi o fare qualcosa.

12. Perdita di interessi
0. Non ho perso interesse verso le altre persone o verso le attività.
1. Sono meno interessato agli altri o alle cose rispetto a prima.
2. Ho perso la maggior parte dell'interesse verso le altre persone o cose.
3. Mi risulta difficile interessarmi a qualsiasi cosa.

13. Indecisione
0. Prendo decisioni come sempre.
1. Trovo più difficoltà del solito nel prendere decisioni.
2. Ho molte più difficoltà nel prendere decisioni rispetto al solito.
3. Non riesco a prendere nessuna decisione.

14. Senso di inutilità
0. Non mi sento inutile.
1. Non mi sento valido e utile come un tempo. 2. Mi sento più inutile delle altre persone.
3. Mi sento completamente inutile. su qualsiasi cosa.

15. Perdita di energia
0. Ho la stessa energia di sempre.
1. Ho meno energia del solito.
2. Non ho energia sufficiente per fare la maggior parte delle cose.
3. Ho così poca energia che non riesco a fare nulla.

16. Sonno
0. Non ho notato alcun cambiamento nel mio modo di dormire.
1a. Dormo un po' più del solito.
1b. Dormo un po' meno del solito.
2a. Dormo molto più del solito.
2b. Dormo molto meno del solito.
3a. Dormo quasi tutto il giorno.
3b. Mi sveglio 1-2 ore prima e non riesco a Riaddormentarmi.

17. Irritabilità
0. Non sono più irritabile del solito.
1. Sono più irritabile del solito.
2. Sono molto più irritabile del solito.
3. Sono sempre irritabile.

18. Appetito
0. Non ho notato alcun cambiamento nel mio appetito.
1a. Il mio appetito è un po' diminuito rispetto al solito.
1b. Il mio appetito è un po' aumentato rispetto al solito
2a. Il mi appetito è molto diminuito rispetto al solito
2b. Il mio appetito è molto aumentato rispetto al solito.
3a. Non ho per niente appetito.
3b. Mangerei in qualsiasi momento

19. Concentrazione
0. Riesco a concentrarmi come sempre.
1. Non riesco a concentrarmi come al solito.
2. Trovo difficile concentrarmi per molto tempo
3. Non riesco a concentrarmi su nulla.

20. Fatica
0. Non sono più stanco o affaticato del solito.
1. Mi stanco e mi affatico più facilmente del solito.
2. Sono così stanco e affaticato che non riesco a fare molte delle cose che facevo prima.
3. Sono talmente stanco e affaticato che non riesco più a fare nessuna delle cos e che facevo prima.

21. Sesso
0. Non ho notato alcun cambiamento recente nel mio interesse verso il sesso.
1. Sono meno interessato al sesso rispetto a prima.
2. Ora sono molto meno interessante al sesso.
3. Ho completamente perso l'interesse verso il sesso.

Scoring
sommare i punteggi ottenuti ai 21 item (ogni item ha un punteggio da 0 a 3) - le risposte a e b ottengono lo stesso punteggio (ad esempio 1a e 1b valgono sempre 1).
Punteggi 0-13 indicano un'assenza di contenuti depressivi;
punteggi compresi tra 14-19: una depressione lieve
punteggi 27-29 una depressione di grado moderato;
punteggi 30- 63: una depressione di grado severo.

FSMC

Scala della Fatica per le Funzioni Motorie e Cognitive

Data: _____

ID: _____

Nome
Cognome:_____

Età: _____

Sesso: m ◯ f ◯

ISTRUZIONI

Il seguente questionario riguarda i problemi della vita quotidina connessi ad un' estrema sensazione di affaticamento. Questa sensazione comprende uno stato di letargia, stanchezza e mancanza di energia che compare improvvisamente in assenza di evidenti cause esterne. Non rientrano gli episodi isolati che tutti potrebbero sperimentare nel corso di una giornata dopo uno sforzo o dopo una nottata insonne! Please read each statement carefully. La invitiamo a leggere con attenzione ogni affermazione in modo da decidere in che misura ciascuna di queste possa essere applicata alla sua vita quotidiana. Provi a non basare le sue risposte sul modo in cui si sente in questo momento; piuttosto cerchi di rispondere sul modo in cui si sente nella normale vita quotidiana. Inserisca una croce nel quadratino che ritiene più appropriato alla sua esperienza (**per ogni affermazione può esserci <u>una sola crocetta</u>!**)

		NON SUCCEDE MAI	NON SUCCEDE QUASI MAI	SUCCEDE POCO	SUCCEDE SPESSO	SUCCEDE SEMPRE
C	1. Quando mi concentro per molto tempo, mi stanco prima delle persone della mia stessa età.	1 ◯	2 ◯	3 ◯	4 ◯	5 ◯
M	2. Quando mi sento stanco e affaticato i miei movimenti diventano notevolemte più goffi e meno coordinati.	◯	◯	◯	◯	◯
M	3. A causa del senso di stanchezza, ho bisogno di fare pause più lunghe e più frequenti durante l'attività fisica rispetto a quanto succedeva in passato.	◯	◯	◯	◯	◯
C	4. Quando mi sento molto stanco e affaticato, sono incapace di prendere decisioni.	◯	◯	◯	◯	◯
M	5. Quando mi trovo ad affrontare situazioni stressanti, il mio fisico si affatica più velocemente di quanto succedeva in passato	◯	◯	◯	◯	◯
M	6. A causa del senso di stanchezza, ho meno contatto sociale di quanto accadeva in passato	◯	◯	◯	◯	◯
C	7. A causa del senso di stanchezza, ho più difficoltà ad imparare cose nuove rispetto a quanto succedeva in passato.	◯	◯	◯	◯	◯

Si prega di girare la paggina

FSMC-cog = _____ FSMC-mot = _____ **FSMC total** = _____

FSMC

		NON SUCCEDE MAI	NON SUCCEDE QUASI MAI	SUCCEDE POCO	SUCCEDE SPESSO	SUCCEDE SEMPRE
C	8. A lavoro la mia mente si stanca più velocemente rispetto a prima.	○	○	○	○	○
M	9. Percepisco la stanchezza e l'affaticamento in maniera molto forte nei muscoli.	○	○	○	○	○
M	10. Non ho più la resistenza e la forza fisica di una volta nello svolgere le attività.	○	○	○	○	○
C	11. La mia capacità di concentrazione diminuisce moltissimo quando sono sotto stress.	○	○	○	○	○
M	12. Quando mi sento esausto ed affaticato, sono meno motivato degli altri ad iniziare attività che richiedono uno sforzo fisico.	○	○	○	○	○
C	13. Quando fa caldo i miei pensieri diventano sempre più lenti.	○	○	○	○	○
M	14. Quando mi sento stanco ed affaticato i miei movimentoi diventano sensibilmente più lenti.	○	○	○	○	○
C	15. A causa del senso di stanchezza, considero le cose che richiedono concentrazione poco piacevoli rispetto al passato.	○	○	○	○	○
M	16. Quando mi capita di sentirmi stanco ed affaticato non riesco a reagire in fretta.	○	○	○	○	○
C	17. Quando sperimento la stanchezza mi scappano direttamente alcune parole.	○	○	○	○	○
C	18. Quando mi sento esausto ed affaticato, perdo velocemente la concentrazione rispetto al mio solito	○	○	○	○	○
M	19. Quando fa caldo il mio sentimento prevalente è un'estrema debolezza fisica ed una mancanza di energia	○	○	○	○	○
C	20. Quando mi sento stanco ed affaticato mi capita spesso di dimenticarmi le cose	○	○	○	○	○

Assicurati di aver compilato tutti i campi del tuo profilo: Nome, Cognome, l'età e il sesso a pagina 1, ed aver messo una croce per ogni istruzione.
Grazie mille.

SYMBOL DIGIT MODALITIES TEST

ISTRUZIONI OPERATIVE

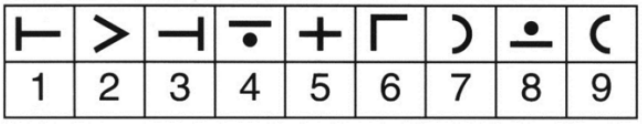
In questa versione orale al paziente viene chiesto di associare a voce il numero corrispondente ad ogni simbolo vedendo la chiave-legenda in alto. L'esaminatore esegue le prime 3 associazioni come esempio, si fa continuare il soggetto con le successive 7 associazioni di prova fino alla doppia linea per familiarizzare con il compito. Dall'undicesima associazione si inizia il conteggio del tempo e dei punteggi corretti.

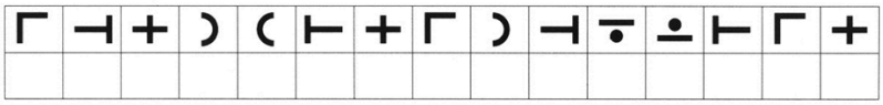
Le istruzioni da fornire sono le seguenti: *"Osservi questi riquadri (indicare la legenda). Come può vedere ogni riquadro è diviso in due parti: in quella superiore c'è un segno, in quella inferiore un numero. Ciascun segno è abbinato ad un numero. Ora osservi qui sotto: come può vedere nel riquadro superiore c'è un segno, mentre il riquadro inferiore è vuoto. Vorrei che lei mi dicesse quale numero deve essere messo in ciascuno dei seguenti riquadri"*. Fare un esempio con i primi tre items, quindi dire: *"Ora, quando le dirò INIZI lei mi dica, il più rapidamente possibile, i numeri da mettere nei singoli riquadri fino alla doppia linea"*. Dare il via, registrare le risposte degli items d'esempio e correggere il soggetto in caso di errore.
Quando gli items d'esempio sono correttamente completati, dire: *"Iniziando dalla doppia linea, mi dica quale numero deve essere messo in ciascun riquadro, per quanti più riquadri può senza saltarne nessuno. Se vuole può tenere il segno con il dito. Quando termina una riga passi subito alla successiva. Lavori il più velocemente possibile, senza fare errori fino a quando la fermerò".*
Dare inizio al test e concedere al soggetto 90 secondi.

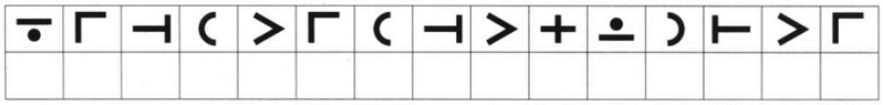
Il punteggio corrisponde al numero delle associazioni corrette e trascritte dall'esaminatore sul foglio delle risposte entro il limite di tempo previsto entro 90 secondi. Il punteggio al SDMT orale varia da 0 a 110.

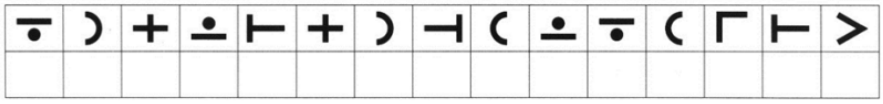
PZ HC Nome e Cognome _____ Sesso _____

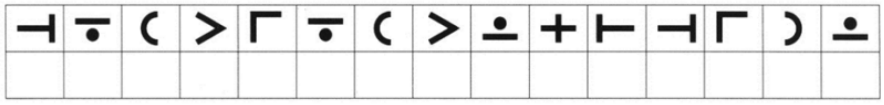
Scolarità in anni _____ Data di nascita _____ Data test_____





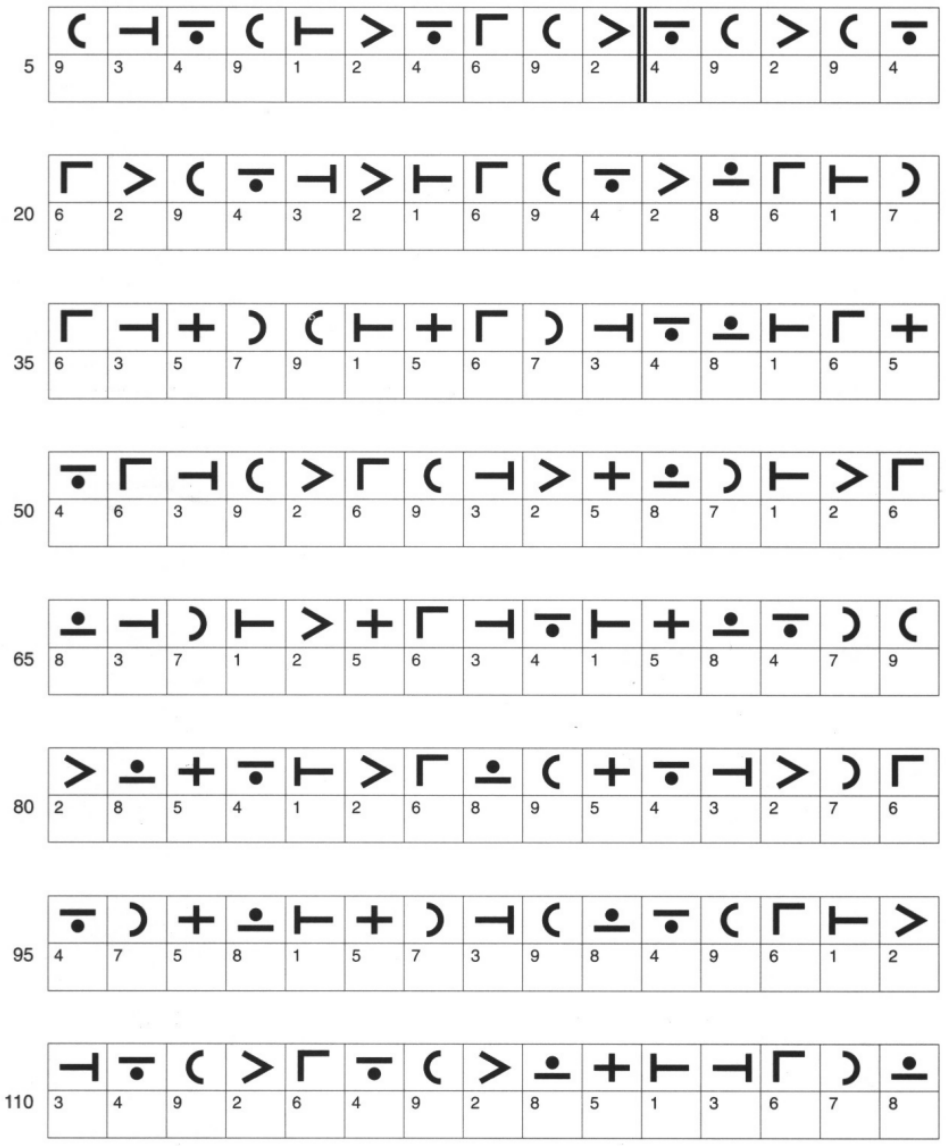






PZ HC Nome e Cognome _____ Sesso _____

Scolarità in anni _____ Data di nascita _____ Data test_____



PZ HC Nome e Cognome _____ Sesso _____

Scolarità in anni _____ Data di nascita _____ Data test_____

CALIFORNIA VERBAL LEARNING TEST-II (CVLT-II)

Somministrazione: leggere la lista di 16 parole al sogg per 5 volte; ogni volta il sogg deve ricordarsi quante più parole possibili in qualsiasi ordine. Ogni volta si deve ripetere al sogg tutte le parole della lista.

Scoring: essendo stata considerata una versione abbreviata del test (sono somministrati solo i primi 5 trials), come punteggio viene calcolato soltanto l'abilità di codifica del materiale ovvero somma delle parole ricordate in ogni trials / numero di trials (5).

LISTA A	1	2	3	4	5	
Camion						
Spinaci						
Giraffa						
Libreria						
Cipolla						
Motocicletta						
Armadietto						
Zebra						
Metropolitana						
Lampada						
Sedano						
Mucca						
Scrivania						
Barca						
Scoiattolo						
Cavolo						
						TOT
Tot. ripetizioni						

PZ HC Nome e Cognome _____ Sesso _____

Scolarità in anni _____ Data di nascita _____ Data test_____

BRIEF VISUOSPATIAL MEMORY TEST REVISED (BVMT-R)

Somministrazione: mostrare al sogg il foglio target con la matrice 2x3 degli stimoli per 10 secondi per 3 volte; ogni volta il sogg dovrà disegnare gli stimoli visti in precedenza con la giusta forma e nella giusta posizione.

Istruzioni:

1. Le mostrerò un foglio su cui sono riportate sei figure. Vorrei che esaminasse le figure in modo da ricordarne quante più possibile. Avrà a disposizione solo 10 secondi per esaminare tutte e sei le figure sul foglio. Le mostrerò qui le figure. Dopo che avrò tolto il foglio su cui sono riportate le sei figure, cerchi di disegnare ciascuna figura esattamente come appare e nella sua posizione corretta sul foglio.
2. Ora disegni quante più figure possibile nella loro posizione corretta sul foglio.
3. Va bene. Ora vorrei che vedesse se riesce a ricordare un numero maggiore delle stesse figure se ha un'altra possibilità. Le mostrerò di nuovo il foglio su cui sono riportate le sei figure per 10 secondi. Cerchi di ricordare quante più figure possibile questa volta, comprese quelle che ha ricordato al suo ultimo tentativo. Cerchi di disegnare ciascuna figura in modo preciso e nella posizione corretta.
4. Va bene. Ora vorrei vedere se riesce a ricordare un numero maggiore delle stesse figure se ha un'altra possibilità. Le mostrerò di nuovo il foglio su cui sono riportate le sei figure per 10 secondi. Cerchi di ricordare quante più figure possibile questa volta, comprese quelle che ha ricordato al suo ultimo tentativo. Cerchi di disegnare ciascuna figura in modo preciso e nella posizione corretta.

Scoring:

Per ognuna delle 6 figure assegnare un punteggio che 0 a 2

Lo score totale sarà un punteggio da 0 a 12.

Score	Accuratezza	Posizione
2	Disegnato accuratamente	Posizionato correttamente
1	Disegnato accuratamente	Posizionato incorrettamente
1	Disegnato in modo impreciso, ma riconoscibile come figura	Posizionato correttamente
0	Non riconoscibile come figura	Posizionato incorrettamente

PZ HC Nome e Cognome _____ Sesso _____

Scolarità in anni _____ Data di nascita _____ Data test_____