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## **MRI characteristics of MOG-Ab associated disease in adults: an update**

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**Abbreviations and Acronyms:**

MOGAD: MOG-Ab associated disease

AQP4-NMOSD: aquaporin-4 antibody neuromyelitis optica spectrum disorder

Ab: antibody

MS: multiple sclerosis

ADEM: acute disseminated encephalomyelitis

ON: optic neuritis

OPN: Optic perineuritis

VA: visual acuity

SM: short myelitis

LETM: longitudinally extensive transverse myelitis

CLIPPERS: chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids

GFAP: glial fibrillary acidic protein

NMDAr: N-methyl-D-aspartate receptor

AMPAr : amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor

GABA<sub>r</sub> : and gamma-aminobutyric acid receptor

DWI : diffusion weighted imaging

PSIR: phase-sensitive inversion-recovery

MPRAGE: magnetization-prepared rapid gradient echo

3D: 3-Dimensional

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1 **MRI characteristics of MOG-Ab associated disease in adults: an update**

2

3 **Abstract:**

4 Our knowledge of the radiological spectrum of myelin oligodendrocyte glycoprotein antibody  
5 associated disease (MOGAD) is growing rapidly. An update on the radiological features of  
6 the disease, and its evolution is thus necessary. Magnetic resonance imaging (MRI) has an  
7 increasingly important role in the differential diagnosis of MOGAD particularly from  
8 aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (AQP4-NMOSD), and  
9 multiple sclerosis (MS). Differentiating these conditions is of prime importance because the  
10 management is different between the three inflammatory diseases, and thus could prevent  
11 further attack-related disability. Therefore, identifying the MRI features suggestive of  
12 MOGAD has diagnostic and prognostic implications. We herein review optic nerve, spinal  
13 cord and the brain MRI findings from MOGAD adult patients, and compare them to AQP4-  
14 NMOSD and MS.

15

16 **Key words:**

17 Imaging

18 Myelin Oligodendrocyte Glycoprotein

19 Aquaporin-4

20 Neuromyelitis Optica

21 Optic neuritis

22 Myelitis

23

24

## 25 **Introduction**

26 The past decades have witnessed important advances in our understanding of neuromyelitis  
27 optica spectrum disorders (NMOSD). Such advances were initiated by the discovery of  
28 disease-specific autoantibodies. The first identified antibody (Ab) was directed against  
29 aquaporin-4 (AQP4-Ab) and led to new set of criteria and the concept of water channel  
30 autoimmunity. More recently, Abs against the myelin oligodendrocyte glycoprotein (MOG-  
31 Ab) have been found in NMOSD patients who tested negative for AQP4-Ab. Emergence of  
32 conformation-dependent serum assays for the detection of MOG-Ab has enabled recognition  
33 of more diverse clinical manifestations and radiological features, different from NMOSD [1].  
34 Evaluating MOG-Ab in the cerebrospinal fluid is promising, but its clinical interest needs to  
35 be validated [2].

36 The clinical phenotype associated with the presence of MOG-Ab changes with age [3] from  
37 acute disseminated encephalomyelitis (ADEM)-related presentation in children, to a more  
38 frequent optico-spinal presentation (optic neuritis, myelitis and brainstem) in adults.

39 Although there are clear phenotypic overlaps between MOG-Ab associated disease  
40 (MOGAD) and multiple sclerosis (MS) or AQP4-NMOSD, cumulative biological, clinical  
41 and pathological evidence clearly discriminates between these conditions. Even though rare,  
42 MOGAD is three times more frequent than AQP4-NMOSD in adults [4], and considered the  
43 second cause of inflammatory optic neuritis after MS [5]. Distinguishing MOGAD from  
44 AQP4-NMOSD and MS is important because evolution and treatment regimens differ  
45 between the three conditions. In addition, a specific MOG-Ab assay is not widely available.

46 Thus, radiological features helping achieve early differentiation between these conditions are  
47 important to establish.

48 We propose herein a review of the literature regarding the radiological features associated  
49 with MOGAD, according to clinical presentation, in comparison to MS and AQP4-NMOSD,  
50 and discuss its most specific characteristics, its evolution and prognostic value, in adults.

## 51 **1. Optic neuritis**

52 MOG-associated optic neuritis (MOG-ON) is the most frequent presentation in adults with  
53 MOGAD [5,6]. It has a slight to moderate female predominance [7,8] and mainly affects  
54 young adults, even if a late age at onset has been reported (up to 79 years old [9]). ON is often  
55 isolated (61% out of 197 patients in the MOGADOR study) [10], more rarely, associated with  
56 myelitis (8%) [10]. A rather frequent simultaneous involvement of both optic nerves (29 to  
57 73%) [11–14] and associated optic disc swelling (70-80%) [15,16] are common during the  
58 first episode of MOG-ON. MOG-ON is also characterized by severe headache at onset,  
59 preceding visual symptoms [17]. Data from prospective cohorts are limited. Despite severe  
60 loss of visual acuity at onset, most recent and large studies found that residual visual  
61 disability is rare: the final visual acuity (VA) was 20/200 or worse in only 6% in a United  
62 States study (median follow-up 2.9 years ) [18], 12% of Sri Lankan patients (4 years) [13],  
63 8% in France (median follow-up 16 months) [10] and in a United Kingdom cohort, 16% had  
64 VA of 6/36 at last follow-up (median follow-up 28 months) [19]. Severe visual impairment  
65 ( $VA \leq 0.1$ ) may occur in the long-term course of the disease in 5% up to 36% of cases  
66 [20,21]. Recurrence is one of the major features of MOG-ON [14,22,23]. Salama et al.  
67 measured an annualized relapsing rate of 0.7 in their cohort with a follow-up of five years  
68 [11]. In the retrospective study by Chen et al. [18] 80% of the 87 patients had two or more

69 attacks of ON (median 3 attacks [1-8]; median follow-up 2.9 years). Finally, MOG-Abs are  
70 found in 25% to 92% of patients with chronic relapsing inflammatory ON [12,24,25].

### 71 **Optic neuritis MRI findings**

72  
73 Typical MOG-ON is identified as optic nerve swelling, with high T2 signal and abnormal  
74 contrast enhancement (Fig.1). MOG-ON is usually described as being extensive (more than a  
75 half of the optic nerve length), bilateral, and anterior [9,15]. It can only rarely be located  
76 within the chiasma or optic tract. MOG-ON is often associated with optic nerve head edema  
77 (48.9% [9] to 80% [16]). Optic perineuritis (OPN), defined as circumferential optic nerve  
78 sheath and orbital fat enhancement, is not rare in MOG-ON [26]. These findings are  
79 summarized in Table 1.

### 80 **Associated MRI findings**

81 In most cases, brain MRI is normal in patients referred for MOG-ON. Even though some  
82 MOGAD patients fulfill dissemination in space and time criteria 11% [9] the association with  
83 MS-like brain lesions is rare (no association in 91.5% [15], 77.2% [9], 89% [8],  
84 respectively). However, “non-specific white matter lesions” were found in patients referred  
85 for ON in 25.5[% 15] to 43.5% [9], which is rather high considering the low median age of  
86 the patients [27]. More rarely, patients show MOGAD-specific brain MRI lesions, mainly  
87 bilateral, in the deep white matter especially in the brainstem [10,15]. Silent spinal cord  
88 involvement was also reported at onset in 10% and 12% of MOG-ON patients [9,20].

### 89 **Evolution**

90 Orbital MRI classically shows regression of nerve swelling and gadolinium enhancement  
91 following intravenous methylprednisolone administration during the acute phase. Follow-up  
92 MRI often reveals a residual T2 hyperintensity, frequently associated with ON atrophy [9].

93 Indeed, contrasting with a rather preserved VA, MRI data have shown important optic nerve  
94 atrophy (90% at one year [9]). This is in line with prior studies highlighting the discrepancy  
95 between visual outcome and optic nerve head thickness measured by optic coherence  
96 tomography [28]. Currently no predictive factor of outcome has been clearly identified in  
97 MOG-ON. In one retrospective study, the strongest MRI predictor of visual prognosis was the  
98 axial ON lesion length in the acute phase for AQP4-NMOSD but no criteria were  
99 significantly related in patients with MOG-ON [29]. Further prospective studies should  
100 determine if the intracanalicular site of the lesion impacts visual recovery, little space in this  
101 segment could contribute to greater axonal compression.

## 102 **Differential diagnosis**

103 The differential diagnosis mainly includes MS-ON, AQP4-NMOSD and idiopathic ON  
104 [5,8,28,30–32]. Some MRI features have been identified to be suggestive of MOG-ON in  
105 comparison with AQP4-NMOSD ON: involvement of the anterior part of the optic pathway,  
106 optic nerve head swelling [8,31]. Conversely, posterior involvement (optic chiasm and optic  
107 tracts) is more frequent in AQP4-NMOSD than in MOG-ON or MS-ON [8,28,30,32]. MOG-  
108 ON or AQP4-NMOSD have been more often associated with a long lesion length (i.e. more  
109 than half of the orbital optic nerve length) [8,30,32] and are more frequently bilateral [8,30]  
110 than seronegative ON or MS-ON. Finally, in case of OPN, inflammatory (sarcoidosis, giant  
111 cell arteritis, anti-neutrophil cytoplasmic Ab vasculitis, IgG4 syndrome), or infectious  
112 (tuberculosis, herpes simplex virus, syphilis) diseases, should be ruled out. Of note, the  
113 association of Leber hereditary optic neuropathy and MOGAD has been reported [33].

114

## 115 **2. Myelitis**



116 Myelitis is the second most frequent presentation in adults with MOGAD. It may occur in  
117 isolation, as a component of ADEM, or concurrently with ON. The clinical features favoring  
118 MOGAD vs AQP4-NMOSD and MS myelitis are male sex, younger age, a prodromal  
119 infectious syndrome (57%), and myelitis occurring as a component of ADEM [34]. When  
120 myelitis is the first manifestation of the disease, it is isolated in around 70% of cases [34]. The  
121 most noticeable clinical features of MOG-Ab myelitis are the high frequency of neurogenic  
122 bladder and/or erectile dysfunction, even if it is not the most frequent symptom. In addition,  
123 20% of patients fulfill criteria for acute flaccid myelitis, usually associated with a viral or  
124 post-viral mechanism [34]. Motor weakness and bladder dysfunction prevalence is higher in  
125 patients with longitudinally extensive transverse myelitis (LETM) compared to short myelitis  
126 [35]. The most frequent type of subsequent attack is isolated optic neuritis (59% within 24-  
127 month follow-up) [34], but recurrences of myelitis are not rare, often with the same myelitis  
128 length [35]. Interestingly, patients with short myelitis had higher annualized relapse rates than  
129 LETM patients (mean: 0.35 vs 0.13). Residual disability depends on the length of myelitis:  
130 patients with LETM were more severe compared to patients with short myelitis [35].  
131 However, residual bladder, bowel and sexual dysfunction are more common than motor  
132 disability.

### 133 **Myelitis MRI findings:**

134 LETM ( $\geq 3$  vertebral segments) is the most frequent imaging hallmark, identified in 61.3% to  
135 92.9% of cases [20,34–36], and often associated with mild cord swelling. The lesions are  
136 mainly located at the cervical and/or thoracic level [20,34,35], but lumbar and conus lesions  
137 are not rare (found in 30.1% to 41%) [34,35]. Cervical myelitis can be associated with  
138 extension to the posterior medulla/area postrema region [35]. T2 hyperintensity is often  
139 confined to spinal cord gray matter, forming an “H sign” in the axial plane and visualized as a

140 line running in the superior-inferior direction on sagittal images [9,34]. When gadolinium  
141 enhancement was noticed, it typically had patchy appearance [20,34]. Pseudo-dilatation of the  
142 ependymal canal has also been proposed as a MOGAD myelitis characteristic feature [37].  
143 Short myelitis, suggestive of MS, has been identified in 38.4% to 48% during the first  
144 MOGAD myelitis episode [35,38], and is more often located in the cervical rather than the  
145 thoracic region and associated with multifocal involvement [20,34,38]. Finally, normal spinal  
146 cord MRI may be a rare but possible feature of MOGAD [20,39,40]. Examples of MOGAD-  
147 associated spinal cord lesions are shown in the Figure 2.

### 148 **Associated MRI findings**

149 Ciron et al. found that the majority (51.4%) of patients had normal brain MRI [35]. Non-  
150 specific white matter lesions were described in 38.9% and MS-like brain lesions were rare,  
151 and not different between LETM and short myelitis (3/44 (6.8%) vs 4/28 (14.3%)).  
152 Interestingly a higher proportion of younger patients (26/38, 68.4%) had an abnormal brain  
153 MRI at onset in comparison with elders (9/34, 26.5%). A recent study by Dubey et al. showed  
154 that 41% of patients had infratentorial and 30% had deep gray matter lesions [34]. In the same  
155 cohort, the patients had up to 30% of lesions consistent with ADEM. This is probably  
156 explained by the mixed (children and adults) population. Anecdotally, paraspinal muscle  
157 involvement has been reported [41].

### 158 **Evolution**

159 Data about radiological follow-up in myelitis of MOGAD are scarce. In line with the good  
160 clinical recovery, spinal cord atrophy is rare. Dubey et al. [34] found only 3% (1/35) of  
161 patients with spinal cord atrophy. Chien et al. [42] found that mean upper cervical cord  
162 atrophy was significantly decreased in AQP4-NMOSD but not in MOGAD. Beyond absence

163 of spinal cord atrophy, complete resolution of T2W high signal have been frequently reported  
164 (36% to 86% of patients) [9,43,44].

165

### 166 **Differential diagnosis**

167 MOGAD and AQP4-NMOSD myelitis share similarities and are known to be rather diffuse,  
168 centrally located and longitudinally extensive; whereas MS-related lesions are often of small  
169 size, affecting the dorsal or lateral columns. A recent study focusing on a mixed population  
170 (adults and children) [34] found no differences in terms of longitudinal extension of spinal  
171 cord lesions between MOGAD and AQP4-NMOSD. However, the inclusion of children may  
172 have influenced the higher proportion of extensive lesions. Conus involvement is more  
173 frequent in MOGAD than AQP4-NMOSD, but did not differ from MS. Lack of gadolinium  
174 enhancement in MOGAD myelitis compared to AQP4-NMOSD [45] and MS [34] has also  
175 been reported. When present, enhancement is often patchy in MOGAD [34] whereas it is  
176 often peripheral in AQP4-NMOSD. Bright spotty lesions, highly suggestive of AQP4-  
177 NMOSD, have only rarely been reported in MOGAD myelitis [42,46]. Finally, frequency of  
178 simultaneous myelitis and ON at disease onset, was much higher in MOGAD (23%) [20] than  
179 in AQP4-NMOSD patients (6.7%) [47].

180

### 181 **3. Brain and brainstem presentation**

182

183 Though it is now well accepted that MOGAD extends beyond optic nerve and spinal cord  
184 lesions, in adult population isolated brain, brainstem or encephalopathic syndromes are rarely  
185 inaugural (6.6% in MOGADOR cohort [10]). Nevertheless, brain lesions in MOGAD can be  
186 roughly separated into three lesion types affecting the brain white matter (focal or diffuse

187 involvement), the brainstem or the cortex. Examples of MOGAD associated brain lesions are  
188 shown in Figures 3 and 4.

189

190

191

### 192 **3.1 Brain white matter involvement**

193 Distinctive brain MRI findings in MOGAD patients (Fig. 4) include the presence of few,  
194 “fluffy” (poorly demarcated) white matter lesions [7,48]. Gadolinium enhancement is  
195 commonly described as nodular or more rarely “open ring” type [46]. Although multiple  
196 series have demonstrated that MOGAD are commonly found in children with ADEM, similar  
197 cases have rarely been described in adult patients, notably in the absence of spinal cord  
198 lesions [10,49]. In addition, some cases of patients with pseudotumoral demyelination have  
199 also been described [50–54] but their exact frequency, specifically in patients with a single  
200 lesion still needs to be determined.

### 201 **Differential diagnosis**

202 Only few MOGAD patients fulfill MRI MS criteria in the majority of studies (11% [9], 4.5%  
203 [55], 1.8% [19], 1.5% [10], 0% [56,57]). Best classifiers for MS vs MOGAD brain lesions  
204 included ovoid lesions adjacent to the body of lateral ventricles, Dawson’s fingers, and T1  
205 hypointense lesions. By contrast, fluffy lesions and less than three lesions are best classifiers  
206 for MOGAD vs MS [48]. Perivascular gadolinium enhancement within white matter lesions  
207 has also been described in MOGAD [58] it could thus mimic primary angitis or encephalitis  
208 associated with glial fibrillary acidic protein (GFAP) astrocytopathy.

209

## 210 **3.2 Brainstem involvement**

211 The incidence of brainstem involvement in MOGAD patients is estimated between 10% and  
212 30% [10,59]. Brainstem symptoms include respiratory insufficiency, intractable  
213 nausea/vomiting, dysarthria, dysphagia, oculomotor nerve palsy, nystagmus, facial nerve  
214 paresis, trigeminal hyperesthesia/dysesthesia, vertigo, hearing loss, balance difficulties, and  
215 gait/limb ataxia. Hypoventilation and respiratory failure may be a more serious picture [59].  
216 The most frequently affected brainstem structure is the pons 34.69% [10], 57% [46], 85%  
217 [60]; followed by the medulla oblongata 14.29% [10], 43% [46], 57% [60]. Brainstem attacks  
218 are often accompanied by acute myelitis and/or ON [60]. Most of the time, brainstem  
219 involvement is associated with good response to corticosteroids, leading to resolution of the  
220 lesions and favorable outcome. More rarely, outside the scope of ADEM, rhombencephalitis  
221 with concomitant extensive brain or spinal cord lesions can be associated with poor prognosis  
222 including fatal outcome [60,61]. Recently the involvement of oculomotor, trigeminal, and  
223 vestibulocochlear cranial nerves has been published [62,63].

## 224 **Differential diagnosis**

225 Poorly delineated lesions in the brainstem or cerebellar peduncles, generally adjacent to the  
226 fourth ventricle, are more likely to occur in MOGAD compared to MS [48]. It remains  
227 challenging to discriminate MOGAD brain lesions from AQP4-NMOSD [64]. However, there  
228 are lesions considered suggestive of AQP4-NMOSD, such as those adjacent to the third  
229 ventricle, periaqueductal or located in area postrema, that are uncommon in MOGAD [65].  
230 MOGAD patients have larger size lesions, with higher probability of cerebellum, pons,  
231 midbrain, gray matter and juxtacortical distribution [64]. Resolution of brain lesions in  
232 MOGAD compared to AQP4-NMOSD is also a feature noted in a few studies [46,48].  
233 Brainstem encephalitis can be attributed to a number of infectious and immune-mediated

234 causes. MOGAD-associated pontine lesions, especially when associated with nodular and  
235 linear contrast enhancement, can mimic chronic lymphocytic inflammation with pontine  
236 perivascular enhancement responsive to steroids (CLIPPERS) [66]. Behcet's disease should  
237 also be considered in a patient with brainstem and basal ganglia lesions.

238

### 239 **3.3 Cortical lesions**

240 Encephalitis and seizure represent 2% to 20% of patients with MOGAD [10,67,68]. It is  
241 probably one of the main causes of autoimmune encephalitis [69]. These episodes are usually  
242 associated with or followed by typical episodes of ON and/or myelitis [10,68,70,71]. Even  
243 though an association with anti-NMDAr (N-methyl-D-aspartate receptor) autoantibodies,  
244 either at the time of encephalitis or after subsequent testing during relapses, has been  
245 described, its frequency is low [72–74].

246 Main radiological features characteristically include unilateral/asymmetrical cortical and/or  
247 leptomeningeal FLAIR hyperintensities that can be associated with gadolinium enhancement  
248 [68,75]. When unilateral, the cortical FLAIR-hyperintense lesion in MOGAD-associated  
249 encephalitis with seizures is referred to as FLAMES [76].

250 Less frequently these encephalopathic presentations have been associated with diffuse  
251 edema, white matter and/or juxtacortical hyperintensities [10,68,70,77]. Very few data on the  
252 clinical and radiological evolution of these patients are available. In the paper by Hamid et al.  
253 [67] four out of five MOGAD patients presenting with encephalopathy and seizures relapsed.  
254 By contrast Ogawa et al. [75] reported an excellent outcome without any relapse and a  
255 complete MRI recovery.

### 256 **Differential diagnosis**

257 To date, no similar syndrome has been described in the setting of MS or AQP4-NMOSD.  
258 Epilepsy is by far more common in the setting of MOGAD (14.7%) vs AQP4-NMOSD (1%).  
259 [67] The main differential diagnoses in those cases are infectious and autoimmune  
260 encephalitis, including amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor  
261 (AMPAr) [69] and gamma-aminobutyric acid receptor (GABA<sub>r</sub>) associated ones [78].  
262 MRI findings in MOGAD comparatively to AQP4-NMOSD and MS patients are summarized  
263 in Table 2 and Figure 5.

#### 264 **Future directions**

265 The broadening of clinical presentation associated with MOGAD is mirrored by the wide  
266 range of neuroimaging findings summarized in this article. However, sensitivity and  
267 specificity of these conventional imaging features for MOGAD have not been systematically  
268 investigated in a prospective manner, and none of the findings can be considered  
269 pathognomonic for MOGAD.

270 We are still lacking prognosis factors for evaluation of MOGAD course and outcome. MOG-  
271 Ab monitoring could be a promising tool as suggested by Waters et al. in a large cohort of  
272 children with MOGAD [79]. It would be highly interesting to assess in parallel the MRI  
273 dynamics along time, and evaluate its potential correlation with MOG-Ab and clinical  
274 activity.

275 Optic nerve imaging remains challenging, mainly because of the eye movement and multiple  
276 artifacts due to the bony structures nearby. Few diffusion-based techniques have been tested  
277 in inflammatory ON. Changes in molecular motion within the optic nerve affected by ON  
278 result in modification in diffusion weighted imaging (DWI) parameters. Thus DWI has also  
279 been studied in the differentiation of NMO from MS-ON with a rather low sensitivity and

280 specificity [80,81]. Recently, diffusional Kurtosis imaging, an extension of the conventional  
281 diffusion tensor imaging model, has shown interesting results in AQP4-NMOSD and could be  
282 tested in MOG-ON [82]. Mainly, the patients have rather preserved final VA but an  
283 important nerve atrophy. That's a particularly striking feature compared to AQP4-NMOSD  
284 patients and needs further research using advanced MRI techniques, such as DWI or  
285 functional connectivity MRI.

286 Spinal cord imaging has recently witnessed some important advances. 3-Dimensional (3D)  
287 phase-sensitive inversion-recovery (PSIR) and magnetization-prepared rapid gradient echo  
288 (MPRAGE) have already been proven useful in MS myelitis [83,84]. 3D spinal cord imaging  
289 permits multiplanar reconstruction and could facilitate the detection of short/silent lesions in  
290 MOGAD. Better long-term outcome and higher rate of spinal cord lesion resolution could be  
291 linked to a less severe tissue destruction in MOGAD myelitis. This feature could be further  
292 explored by spinal cord spectroscopy as it was done in AQP4-NMOSD and MS [85]. The rate  
293 of spinal cord atrophy can become an important outcome measure in clinical trials. Recent  
294 developments allow the calculation of spinal cord atrophy from brain volumetric scans and  
295 evaluation of its progression over time with registration-based techniques.

296 Overall, areas of improvement of imaging, that may facilitate more specific diagnosis,  
297 prognosis, and therapeutic accuracy include higher-resolution imaging methods, 3-  
298 dimensional imaging of site-specific lesions (spinal cord and optic nerves), and potential  
299 computationally guided analysis of images for quantitative comparisons. Developing  
300 algorithms using the brain criteria in combination with spinal cord and optic nerve imaging  
301 features and possibly non-conventional imaging may further improve the sensitivity and  
302 specificity.

303 It is to notice that advanced MRI techniques remain technically challenging, and results from  
304 studies using different acquisition protocols are difficult to compare, thus it is important to  
305 have a standard protocol with robust sequences covering the anterior visual pathway, the brain



306 and the spinal cord, for long-term prospective systematic imaging studies in MOGAD. In  
307 parallel to this need for imaging protocol standardization, the creation of a national registry of  
308 standardized recorded demographic and clinical data, associated with biobanked standardized  
309 samples, are mandatory to further characterize this new but rare disease. This effort has  
310 already been launched in several countries, including France, with the MOGADOR cohort  
311 under the aegis of OFSEP (*Observatoire Français de la Sclérose en Plaques*) [10].

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#### 317 REFERENCES:

- 318 [1] López-Chiriboga AS, Majed M, Fryer J, Dubey D, McKeon A, Flanagan EP, et al.  
319 Association of MOG-IgG Serostatus With Relapse After Acute Disseminated  
320 Encephalomyelitis and Proposed Diagnostic Criteria for MOG-IgG-Associated Disorders.  
321 JAMA Neurol 2018;75:1355–63. <https://doi.org/10.1001/jamaneurol.2018.1814>.
- 322 [2] Mariotto S, Gajofatto A, Batzu L, Delogu R, Sechi G, Leoni S, et al. Relevance of  
323 antibodies to myelin oligodendrocyte glycoprotein in CSF of seronegative cases. Neurology  
324 2019;10.1212/WNL.0000000000008479. <https://doi.org/10.1212/WNL.0000000000008479>.
- 325 [3] Reindl M, Waters P. Myelin oligodendrocyte glycoprotein antibodies in neurological  
326 disease. Nat Rev Neurol 2019;15:89–102. <https://doi.org/10.1038/s41582-018-0112-x>.
- 327 [4] Kunchok A, Chen JJ, McKeon A, Mills JR, Flanagan EP, Pittock SJ. Coexistence of  
328 Myelin Oligodendrocyte Glycoprotein and Aquaporin-4 Antibodies in Adult and Pediatric  
329 Patients. JAMA Neurol 2020;77:257–9. <https://doi.org/10.1001/jamaneurol.2019.3656>.
- 330 [5] Deschamps R, Lecler A, Lamirel C, Aboab J, Gueguen A, Bensa C, et al. Etiologies of  
331 acute demyelinating optic neuritis: an observational study of 110 patients. Eur J Neurol  
332 2017;24:875–9. <https://doi.org/10.1111/ene.13315>.
- 333 [6] Ducloyer J-B, Caignard A, Aidaoui R, Ollivier Y, Plubeau G, Santos-Moskalyk S, et  
334 al. MOG-Ab prevalence in optic neuritis and clinical predictive factors for diagnosis. Br J  
335 Ophthalmol 2019. <https://doi.org/10.1136/bjophthalmol-2019-314845>.
- 336 [7] Zhou Y, Jia X, Yang H, Chen C, Sun X, Peng L, et al. Myelin oligodendrocyte  
337 glycoprotein antibody-associated demyelination: comparison between onset phenotypes. Eur J  
338 Neurol 2019;26:175–83. <https://doi.org/10.1111/ene.13791>.
- 339 [8] Ramanathan S, Prelog K, Barnes EH, Tantsis EM, Reddel SW, Henderson APD, et al.  
340 Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein  
341 antibodies, aquaporin-4 antibodies, and multiple sclerosis. Mult Scler 2016;22:470–82.  
342 <https://doi.org/10.1177/1352458515593406>.
- 343 [9] Shor N, Aboab J, Maillart E, Lecler A, Bensa C, Le Guern G, et al. Clinical, imaging  
344 and follow-up study of optic neuritis associated with myelin oligodendrocyte glycoprotein  
345 antibody: a multicentre study of 62 adult patients. Eur J Neurol 2020;27:384–91.  
346 <https://doi.org/10.1111/ene.14089>.

- 347 [10] Cobo-Calvo A, Ruiz A, Maillart E, Audoin B, Zephir H, Bourre B, et al. Clinical  
348 spectrum and prognostic value of CNS MOG autoimmunity in adults: The MOGADOR  
349 study. *Neurology* 2018;90:e1858–69. <https://doi.org/10.1212/WNL.0000000000005560>.
- 350 [11] Salama S, Pardo S, Levy M. Clinical characteristics of myelin oligodendrocyte  
351 glycoprotein antibody neuromyelitis optica spectrum disorder. *Mult Scler Relat Disord*  
352 2019;30:231–5. <https://doi.org/10.1016/j.msard.2019.02.023>.
- 353 [12] Liu H, Zhou H, Wang J, Sun M, Teng D, Song H, et al. The prevalence and prognostic  
354 value of myelin oligodendrocyte glycoprotein antibody in adult optic neuritis. *J Neurol Sci*  
355 2019;396:225–31. <https://doi.org/10.1016/j.jns.2018.11.029>.
- 356 [13] Senanayake B, Jitprapaikulsan J, Aravinthan M, Wijesekera JC, Ranawaka UK, Riffsy  
357 MT, et al. Seroprevalence and clinical phenotype of MOG-IgG-associated disorders in Sri  
358 Lanka. *J Neurol Neurosurg Psychiatry* 2019;90:1381–3. <https://doi.org/10.1136/jnnp-2018-320243>.
- 360 [14] Song H, Zhou H, Yang M, Wang J, Liu H, Sun M, et al. Different Characteristics of  
361 Aquaporin-4 and Myelin Oligodendrocyte Glycoprotein Antibody-Seropositive Male Optic  
362 Neuritis in China. *J Ophthalmol* 2019;2019:4015075. <https://doi.org/10.1155/2019/4015075>.
- 363 [15] Biotti D, Bonneville F, Tournaire E, Ayrignac X, Dallièrè CC, Mahieu L, et al. Optic  
364 neuritis in patients with anti-MOG antibodies spectrum disorder: MRI and clinical features  
365 from a large multicentric cohort in France. *J Neurol* 2017;264:2173–5.  
366 <https://doi.org/10.1007/s00415-017-8615-8>.
- 367 [16] Zhao Y, Tan S, Chan TCY, Xu Q, Zhao J, Teng D, et al. Clinical features of  
368 demyelinating optic neuritis with seropositive myelin oligodendrocyte glycoprotein antibody  
369 in Chinese patients. *Br J Ophthalmol* 2018;102:1372–7. <https://doi.org/10.1136/bjophthalmol-2017-311177>.
- 371 [17] Asseger S, Hamblin J, Messina S, Mariano R, Siebert N, Everett R, et al. Prodromal  
372 headache in MOG-antibody positive optic neuritis. *Mult Scler Relat Disord* 2020;40:101965.  
373 <https://doi.org/10.1016/j.msard.2020.101965>.
- 374 [18] Chen JJ, Flanagan EP, Jitprapaikulsan J, López-Chiriboga ASS, Fryer JP, Leavitt JA,  
375 et al. Myelin Oligodendrocyte Glycoprotein Antibody-Positive Optic Neuritis: Clinical  
376 Characteristics, Radiologic Clues, and Outcome. *Am J Ophthalmol* 2018;195:8–15.  
377 <https://doi.org/10.1016/j.ajo.2018.07.020>.
- 378 [19] Jurynczyk M, Messina S, Woodhall MR, Raza N, Everett R, Roca-Fernandez A, et al.  
379 Clinical presentation and prognosis in MOG-antibody disease: a UK study. *Brain*  
380 2017;140:3128–38. <https://doi.org/10.1093/brain/awx276>.
- 381 [20] Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, et al. MOG-IgG in  
382 NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical  
383 presentation, radiological and laboratory features, treatment responses, and long-term  
384 outcome. *J Neuroinflammation* 2016;13:280. <https://doi.org/10.1186/s12974-016-0718-0>.
- 385 [21] Sepúlveda M, Armangue T, Martinez-Hernandez E, Arrambide G, Sola-Valls N,  
386 Sabater L, et al. Clinical spectrum associated with MOG autoimmunity in adults: significance  
387 of sharing rodent MOG epitopes. *J Neurol* 2016;263:1349–60.  
388 <https://doi.org/10.1007/s00415-016-8147-7>.
- 389 [22] Kim S-M, Woodhall MR, Kim J-S, Kim S-J, Park KS, Vincent A, et al. Antibodies to  
390 MOG in adults with inflammatory demyelinating disease of the CNS. *Neurol Neuroimmunol*  
391 *Neuroinflamm* 2015;2:e163. <https://doi.org/10.1212/NXI.0000000000000163>.
- 392 [23] Chalmoukou K, Alexopoulos H, Akrivou S, Stathopoulos P, Reindl M, Dalakas MC.  
393 Anti-MOG antibodies are frequently associated with steroid-sensitive recurrent optic neuritis.  
394 *Neurol Neuroimmunol Neuroinflamm* 2015;2:e131.  
395 <https://doi.org/10.1212/NXI.0000000000000131>.
- 396 [24] Lee H-J, Kim B, Waters P, Woodhall M, Irani S, Ahn S, et al. Chronic relapsing

397 inflammatory optic neuropathy (CRION): a manifestation of myelin oligodendrocyte  
398 glycoprotein antibodies. *J Neuroinflammation* 2018;15. [https://doi.org/10.1186/s12974-018-](https://doi.org/10.1186/s12974-018-1335-x)  
399 1335-x.

400 [25] Petzold A, Plant GT. Chronic relapsing inflammatory optic neuropathy: a systematic  
401 review of 122 cases reported. *J Neurol* 2014;261:17–26. [https://doi.org/10.1007/s00415-013-](https://doi.org/10.1007/s00415-013-6957-4)  
402 6957-4.

403 [26] Purvin V, Kawasaki A, Jacobson DM. Optic Perineuritis: Clinical and Radiographic  
404 Features. *Arch Ophthalmol* 2001;119:1299–306. <https://doi.org/10.1001/archoph.119.9.1299>.

405 [27] Uggetti C, Squarza S, Longaretti F, Galli A, Di Fiore P, Reganati PF, et al. Migraine  
406 with aura and white matter lesions: an MRI study. *Neurological Sciences* 2017;38:11–3.  
407 <https://doi.org/10.1007/s10072-017-2897-6>.

408 [28] Deschamps R, Gueguen A, Lecler A, Lecouturier K, Lamirel C, Bensa C, et al. Acute  
409 idiopathic optic neuritis: not always benign. *European Journal of Neurology* 2018;25:1378–  
410 83. <https://doi.org/10.1111/ene.13753>.

411 [29] Akaishi T, Nakashima I, Takeshita T, Mugikura S, Sato DK, Takahashi T, et al.  
412 Lesion length of optic neuritis impacts visual prognosis in neuromyelitis optica. *J*  
413 *Neuroimmunol* 2016;293:28–33. <https://doi.org/10.1016/j.jneuroim.2016.02.004>.

414 [30] Akaishi T, Sato DK, Nakashima I, Takeshita T, Takahashi T, Doi H, et al. MRI and  
415 retinal abnormalities in isolated optic neuritis with myelin oligodendrocyte glycoprotein and  
416 aquaporin-4 antibodies: a comparative study. *J Neurol Neurosurg Psychiatry* 2016;87:446–8.  
417 <https://doi.org/10.1136/jnnp-2014-310206>.

418 [31] Chen C, Liu C, Fang L, Zou Y, Ruan H, Wang Y, et al. Different magnetic resonance  
419 imaging features between MOG antibody- and AQP4 antibody-mediated disease: A Chinese  
420 cohort study. *Journal of the Neurological Sciences* 2019;405.  
421 <https://doi.org/10.1016/j.jns.2019.116430>.

422 [32] Ishikawa H, Kezuka T, Shikishima K, Yamagami A, Hiraoka M, Chuman H, et al.  
423 Epidemiologic and Clinical Characteristics of Optic Neuritis in Japan. *Ophthalmology*  
424 2019;126:1385–98. <https://doi.org/10.1016/j.ophtha.2019.04.042>.

425 [33] Bittner F, Falardeau J, Spain RI. Myelin Oligodendrocyte Glycoprotein Antibody–  
426 Associated Demyelination Comorbid With Leber Hereditary Optic Neuropathy. *JAMA*  
427 *Neurol* 2019;76:227–8. <https://doi.org/10.1001/jamaneurol.2018.3207>.

428 [34] Dubey D, Pittock SJ, Krecke KN, Morris PP, Sechi E, Zaleski NL, et al. Clinical,  
429 Radiologic, and Prognostic Features of Myelitis Associated With Myelin Oligodendrocyte  
430 Glycoprotein Autoantibody. *JAMA Neurol* 2018.  
431 <https://doi.org/10.1001/jamaneurol.2018.4053>.

432 [35] Ciron J, Cobo-Calvo A, Audoin B, Bourre B, Brassat D, Cohen M, et al. Frequency  
433 and characteristics of short versus longitudinally extensive myelitis in adults with MOG  
434 antibodies: A retrospective multicentric study. *Mult Scler* 2019:1352458519849511.  
435 <https://doi.org/10.1177/1352458519849511>.

436 [36] Baumann M, Sahin K, Lechner C, Hennes EM, Schanda K, Mader S, et al. Clinical  
437 and neuroradiological differences of paediatric acute disseminating encephalomyelitis with  
438 and without antibodies to the myelin oligodendrocyte glycoprotein. *J Neurol Neurosurg*  
439 *Psychiatry* 2015;86:265–72. <https://doi.org/10.1136/jnnp-2014-308346>.

440 [37] Denève M, Biotti D, Patsoura S, Ferrier M, Meluchova Z, Mahieu L, et al. MRI  
441 features of demyelinating disease associated with anti-MOG antibodies in adults. *J*  
442 *Neuroradiol* 2019;46:312–8. <https://doi.org/10.1016/j.neurad.2019.06.001>.

443 [38] Mariano R, Messina S, Kumar K, Kuker W, Leite MI, Palace J. Comparison of  
444 Clinical Outcomes of Transverse Myelitis Among Adults With Myelin Oligodendrocyte  
445 Glycoprotein Antibody vs Aquaporin-4 Antibody Disease. *JAMA Netw Open*  
446 2019;2:e1912732. <https://doi.org/10.1001/jamanetworkopen.2019.12732>.

447 [39] Macaron G, Ontaneda D. MOG-related disorders: A new cause of imaging-negative  
448 myelitis? *Mult Scler* 2019;1352458519840746. <https://doi.org/10.1177/1352458519840746>.

449 [40] Sechi E, Krecke KN, Pittock SJ, Dubey D, Lopez-Chiriboga AS, Kunchok A, et al.  
450 Frequency and characteristics of MRI-negative myelitis associated with MOG autoantibodies.  
451 *Mult Scler* 2020;1352458520907900. <https://doi.org/10.1177/1352458520907900>.

452 [41] Pandit L, Mustafa S, Uppoor R, Nakashima I, Takahashi T, Kaneko K. Reversible  
453 paraspinal muscle hyperintensity in anti-MOG antibody-associated transverse myelitis.  
454 *Neurol Neuroimmunol Neuroinflamm* 2017;5.  
455 <https://doi.org/10.1212/NXI.0000000000000412>.

456 [42] Chien C, Scheel M, Schmitz-Hübsch T, Borisow N, Ruprecht K, Bellmann-Strobl J, et  
457 al. Spinal cord lesions and atrophy in NMOSD with AQP4-IgG and MOG-IgG associated  
458 autoimmunity. *Mult Scler* 2018;1352458518815596.  
459 <https://doi.org/10.1177/1352458518815596>.

460 [43] Cobo-Calvo Á, Sepúlveda M, Bernard-Valnet R, Ruiz A, Brassat D, Martínez-  
461 Yélamos S, et al. Antibodies to myelin oligodendrocyte glycoprotein in aquaporin 4 antibody  
462 seronegative longitudinally extensive transverse myelitis: Clinical and prognostic  
463 implications. *Mult Scler* 2016;22:312–9. <https://doi.org/10.1177/1352458515591071>.

464 [44] Kitley J, Waters P, Woodhall M, Leite MI, Murchison A, George J, et al.  
465 Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte  
466 glycoprotein antibodies: a comparative study. *JAMA Neurol* 2014;71:276–83.  
467 <https://doi.org/10.1001/jamaneurol.2013.5857>.

468 [45] Loos J, Pfeuffer S, Pape K, Ruck T, Luessi F, Spreer A, et al. MOG  
469 encephalomyelitis: distinct clinical, MRI and CSF features in patients with longitudinal  
470 extensive transverse myelitis as first clinical presentation. *J Neurol* 2020.  
471 <https://doi.org/10.1007/s00415-020-09755-x>.

472 [46] Salama S, Khan M, Levy M, Izbudak I. Radiological characteristics of myelin  
473 oligodendrocyte glycoprotein antibody disease. *Mult Scler Relat Disord* 2019;29:15–22.  
474 <https://doi.org/10.1016/j.msard.2019.01.021>.

475 [47] Jarius S, Ruprecht K, Wildemann B, Kuempfel T, Ringelstein M, Geis C, et al.  
476 Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A  
477 multicentre study of 175 patients. *J Neuroinflammation* 2012;9:14.  
478 <https://doi.org/10.1186/1742-2094-9-14>.

479 [48] Jurynczyk M, Gheraldes R, Probert F, Woodhall MR, Waters P, Tackley G, et al.  
480 Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple  
481 sclerosis. *Brain* 2017;140:617–27. <https://doi.org/10.1093/brain/aww350>.

482 [49] Hamid SHM, Whittam D, Saviour M, Alorainy A, Mutch K, Linaker S, et al. Seizures  
483 and Encephalitis in Myelin Oligodendrocyte Glycoprotein IgG Disease vs Aquaporin 4 IgG  
484 Disease. *JAMA Neurol* 2018;75:65–71. <https://doi.org/10.1001/jamaneurol.2017.3196>.

485 [50] Miyae N, Yamanishi Y, Tada S, Ando R, Yabe H, Nagai M, et al. A case of ADEM-  
486 like presentation with anti-MOG antibody following tumefactive demyelinating lesion. *Mult*  
487 *Scler Relat Disord* 2019;31:62–4. <https://doi.org/10.1016/j.msard.2019.03.018>.

488 [51] Hardy TA. Pseudotumoral demyelinating lesions: diagnostic approach and long-term  
489 outcome. *Curr Opin Neurol* 2019;32:467–74.  
490 <https://doi.org/10.1097/WCO.0000000000000683>.

491 [52] Di Pauli F, Höftberger R, Reindl M, Beer R, Rhomberg P, Schanda K, et al. Fulminant  
492 demyelinating encephalomyelitis: Insights from antibody studies and neuropathology. *Neurol*  
493 *Neuroimmunol Neuroinflamm* 2015;2:e175. <https://doi.org/10.1212/NXI.0000000000000175>.

494 [53] Shu Y, Long Y, Wang S, Hu W, Zhou J, Xu H, et al. Brain histopathological study  
495 and prognosis in MOG antibody-associated demyelinating pseudotumor. *Ann Clin Transl*  
496 *Neurol* 2019;6:392–6. <https://doi.org/10.1002/acn3.712>.

- 497 [54] Katsuse K, Kurihara M, Sugiyama Y, Kodama S, Takahashi M, Momose T, et al.  
498 Aphasic status epilepticus preceding tumefactive left hemisphere lesion in anti-MOG  
499 antibody associated disease. *Mult Scler Relat Disord* 2019;27:91–4.  
500 <https://doi.org/10.1016/j.msard.2018.10.012>.
- 501 [55] Mariotto S, Ferrari S, Monaco S, Benedetti MD, Schanda K, Alberti D, et al. Clinical  
502 spectrum and IgG subclass analysis of anti-myelin oligodendrocyte glycoprotein antibody-  
503 associated syndromes: a multicenter study. *J Neurol* 2017;264:2420–30.  
504 <https://doi.org/10.1007/s00415-017-8635-4>.
- 505 [56] Oliveira LM, Apóstolos-Pereira SL, Pitombeira MS, Bruel Torretta PH, Callegaro D,  
506 Sato DK. Persistent MOG-IgG positivity is a predictor of recurrence in MOG-IgG-associated  
507 optic neuritis, encephalitis and myelitis. *Mult Scler* 2018;1352458518811597.  
508 <https://doi.org/10.1177/1352458518811597>.
- 509 [57] Jitrapaikulsan J, Chen JJ, Flanagan EP, Tobin WO, Fryer JP, Weinshenker BG, et al.  
510 Aquaporin-4 and Myelin Oligodendrocyte Glycoprotein Autoantibody Status Predict  
511 Outcome of Recurrent Optic Neuritis. *Ophthalmology* 2018;125:1628–37.  
512 <https://doi.org/10.1016/j.ophtha.2018.03.041>.
- 513 [58] Komatsu T, Matsushima S, Kaneko K, Fukuda T. Perivascular enhancement in anti-  
514 MOG antibody demyelinating disease of the CNS. *J Neurol Neurosurg Psychiatry*  
515 2019;90:111–2. <https://doi.org/10.1136/jnnp-2018-319235>.
- 516 [59] Jarius S, Kleiter I, Ruprecht K, Asgari N, Pitarokoili K, Borisow N, et al. MOG-IgG in  
517 NMO and related disorders: a multicenter study of 50 patients. Part 3: Brainstem involvement  
518 - frequency, presentation and outcome. *J Neuroinflammation* 2016;13:281.  
519 <https://doi.org/10.1186/s12974-016-0719-z>.
- 520 [60] Jarius S, Kleiter I, Ruprecht K, Asgari N, Pitarokoili K, Borisow N, et al. MOG-IgG in  
521 NMO and related disorders: a multicenter study of 50 patients. Part 3: Brainstem involvement  
522 - frequency, presentation and outcome. *J Neuroinflammation* 2016;13.  
523 <https://doi.org/10.1186/s12974-016-0719-z>.
- 524 [61] Vecchio D, Virgilio E, Naldi P, Comi C, Cantello R. MOG-antibody demyelinating  
525 diseases: a case of post-partum severe rhombencephalitis and transverse myelitis. *Mult Scler*  
526 *Relat Disord* 2018;21:9–10. <https://doi.org/10.1016/j.msard.2018.02.006>.
- 527 [62] Cobo-Calvo A, Ayrignac X, Kerschen P, Horellou P, Cotton F, Labauge P, et al.  
528 Cranial nerve involvement in patients with MOG antibody-associated disease. *Neurol*  
529 *Neuroimmunol Neuroinflamm* 2019;6:e543. <https://doi.org/10.1212/NXI.0000000000000543>.
- 530 [63] Shen Y, Cheng Z, Zhou C. Bilateral trigeminal root entry zone enhancement in MOG-  
531 IgG-associated brainstem encephalitis. *Neurol Sci* 2019;40:1083–5.  
532 <https://doi.org/10.1007/s10072-018-3668-8>.
- 533 [64] Yang L, Li H, Xia W, Quan C, Zhou L, Geng D, et al. Quantitative brain lesion  
534 distribution may distinguish MOG-ab and AQP4-ab neuromyelitis optica spectrum disorders.  
535 *Eur Radiol* 2019. <https://doi.org/10.1007/s00330-019-06506-z>.
- 536 [65] Kunchok A, Krecke K, Flanagan E, Jitrapaikulsan J, Lopez-Chiriboga A, Chen J, et  
537 al. Does area postrema syndrome occur in myelin oligodendrocyte glycoprotein-IgG-  
538 associated disorders (MOGAD)? *Neurology* 2019;94.  
539 <https://doi.org/10.1212/WNL.00000000000008786>.
- 540 [66] Berzero G, Taieb G, Marignier R, Younan N, Savatovsky J, Leclercq D, et al.  
541 CLIPPERS mimickers: relapsing brainstem encephalitis associated with anti-MOG  
542 antibodies. *Eur J Neurol* 2018;25:e16–7. <https://doi.org/10.1111/ene.13483>.
- 543 [67] Hamid SHM, Whittam D, Saviour M, Alorainy A, Mutch K, Linaker S, et al. Seizures  
544 and Encephalitis in Myelin Oligodendrocyte Glycoprotein IgG Disease vs Aquaporin 4 IgG  
545 Disease. *JAMA Neurol* 2018;75:65–71. <https://doi.org/10.1001/jamaneurol.2017.3196>.
- 546 [68] Wang L, Zhang Bao J, Zhou L, Zhang Y, Li H, Li Y, et al. Encephalitis is an important

547 clinical component of myelin oligodendrocyte glycoprotein antibody associated  
548 demyelination: a single-center cohort study in Shanghai, China. *Eur J Neurol* 2019;26:168–  
549 74. <https://doi.org/10.1111/ene.13790>.

550 [69] Dubey D, Pittock SJ, Kelly CR, McKeon A, Lopez-Chiriboga AS, Lennon VA, et al.  
551 Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. *Ann*  
552 *Neurol* 2018;83:166–77. <https://doi.org/10.1002/ana.25131>.

553 [70] Fujimori J, Takai Y, Nakashima I, Sato DK, Takahashi T, Kaneko K, et al. Bilateral  
554 frontal cortex encephalitis and paraparesis in a patient with anti-MOG antibodies. *J Neurol*  
555 *Neurosurg Psychiatry* 2017;88:534–6. <https://doi.org/10.1136/jnnp-2016-315094>.

556 [71] Haddad N, Roussel B, Pelcovits A, Rizvi S. Optic neuritis, encephalitis and  
557 leptomeningeal enhancement in a patient with anti-MOG antibodies: A case study. *Multiple*  
558 *Sclerosis and Related Disorders* 2019;34:14–6. <https://doi.org/10.1016/j.msard.2019.06.010>.

559 [72] Titulaer MJ, Höftberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, et al.  
560 Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis.  
561 *Ann Neurol* 2014;75:411–28. <https://doi.org/10.1002/ana.24117>.

562 [73] Ramberger M, Bsteh G, Schanda K, Höftberger R, Rostásy K, Baumann M, et al.  
563 NMDA receptor antibodies: A rare association in inflammatory demyelinating diseases.  
564 *Neurol Neuroimmunol Neuroinflamm* 2015;2:e141.  
565 <https://doi.org/10.1212/NXI.0000000000000141>.

566 [74] Ren Y, Chen X, He Q, Wang R, Lu W. Co-occurrence of Anti-N-Methyl-D-Aspartate  
567 Receptor Encephalitis and Anti-myelin Oligodendrocyte Glycoprotein Inflammatory  
568 Demyelinating Diseases: A Clinical Phenomenon to Be Taken Seriously. *Front Neurol*  
569 2019;10. <https://doi.org/10.3389/fneur.2019.01271>.

570 [75] Ogawa R, Nakashima I, Takahashi T, Kaneko K, Akaishi T, Takai Y, et al. MOG  
571 antibody-positive, benign, unilateral, cerebral cortical encephalitis with epilepsy. *Neurol*  
572 *Neuroimmunol Neuroinflamm* 2017;4. <https://doi.org/10.1212/NXI.0000000000000322>.

573 [76] Budhram A, Mirian A, Le C, Hosseini-Moghaddam SM, Sharma M, Nicolle MW.  
574 Unilateral cortical FLAIR-hyperintense Lesions in Anti-MOG-associated Encephalitis with  
575 Seizures (FLAMES): characterization of a distinct clinico-radiographic syndrome. *J Neurol*  
576 2019;266:2481–7. <https://doi.org/10.1007/s00415-019-09440-8>.

577 [77] Fujimori J, Takahashi T, Matsumoto Y, Fujihara K, Takai Y, Misu T, et al. Two  
578 Japanese cases of anti-MOG antibody-associated encephalitis that mimicked neuro-Behçet’s  
579 disease. *J Neuroimmunol* 2019;334:577002. <https://doi.org/10.1016/j.jneuroim.2019.577002>.

580 [78] Spatola M, Petit-Pedrol M, Simabukuro MM, Armangue T, Castro FJ, Barcelo  
581 Artigues MI, et al. Investigations in GABAA receptor antibody-associated encephalitis.  
582 *Neurology* 2017;88:1012–20. <https://doi.org/10.1212/WNL.0000000000003713>.

583 [79] Waters P, Fadda G, Woodhall M, O’Mahony J, Brown RA, Castro DA, et al. Serial  
584 Anti-Myelin Oligodendrocyte Glycoprotein Antibody Analyses and Outcomes in Children  
585 With Demyelinating Syndromes. *JAMA Neurol* 2020;77:82–93.  
586 <https://doi.org/10.1001/jamaneurol.2019.2940>.

587 [80] Wan H, He H, Zhang F, Sha Y, Tian G. Diffusion-weighted imaging helps  
588 differentiate multiple sclerosis and neuromyelitis optica-related acute optic neuritis. *J Magn*  
589 *Reson Imaging* 2017;45:1780–5. <https://doi.org/10.1002/jmri.25528>.

590 [81] Lu P, Tian G, Liu X, Wang F, Zhang Z, Sha Y. Differentiating Neuromyelitis Optica-  
591 Related and Multiple Sclerosis-Related Acute Optic Neuritis Using Conventional Magnetic  
592 Resonance Imaging Combined With Readout-Segmented Echo-Planar Diffusion-Weighted  
593 Imaging. *J Comput Assist Tomogr* 2018;42:502–9.  
594 <https://doi.org/10.1097/RCT.0000000000000724>.

595 [82] Lu P, Yuan T, Liu X, Tian G, Zhang J, Sha Y. Role of Diffusional Kurtosis Imaging in  
596 Differentiating Neuromyelitis Optica-Related and Multiple Sclerosis-Related Acute Optic

597 Neuritis: Comparison With Diffusion-Weighted Imaging. *J Comput Assist Tomogr*  
598 2020;44:47–52. <https://doi.org/10.1097/RCT.0000000000000974>.

599 [83] Mirafzal S, Goujon A, Deschamps R, Zuber K, Sadik JC, Gout O, et al. 3D PSIR MRI  
600 at 3 Tesla improves detection of spinal cord lesions in multiple sclerosis. *J Neurol* 2019.  
601 <https://doi.org/10.1007/s00415-019-09591-8>.

602 [84] Nair G, Absinta M, Reich DS. Optimized T1-MPRAGE sequence for better  
603 visualization of spinal cord multiple sclerosis lesions at 3T. *AJNR Am J Neuroradiol*  
604 2013;34:2215–22. <https://doi.org/10.3174/ajnr.A3637>.

605 [85] Ciccarelli O, Thomas DL, De Vita E, Wheeler-Kingshott CAM, Kachramanoglou C,  
606 Kapoor R, et al. Low myo-inositol indicating astrocytic damage in a case series of  
607 neuromyelitis optica. *Ann Neurol* 2013;74:301–5. <https://doi.org/10.1002/ana.23909>.

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619 **Table 1: Clinical and orbital MRI characteristics of MOG-Ab associated ON**

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	Ramanathan and al. 2016[8]	Akaishi and al. 2016[30]	Zhao and al. 2018[16]	Chen and al. 2018[18]	Liu and al. 2019[12]	Song and al. 2019[14]	Salama and al.[46] 2019	Shor and al. 2019[9]
Number of patients	19	13	20	50	21 AE	70AE*	18	62
Bilateral ON, %	NA	30.8	45	37	29	29.5**	NA	41.9
Gadolinium enhancement, %	94	82.4	80	100	NA	NA	100%	93.1
Optic nerve head edema, %	53	NA	80	NA	NA	NA	NA	48.9
Optic perineurtis, %	89	47.1	NA	50	NA	NA	NA	46.6
Intra-orbital involvement, %	53	73.7	80	92	95.2	95.7	88.3	92
Canalicular involvement, %	16	100	30	72	85.7	75.9	58.3	71.6
Intracranial involvement, %	32	100	15		38.1	42.9	41.7	
Chiasm involvement, %	5	0	15	12	9.5	11.6	8.3	6.4
Optic tract involvement, %	0	0	5	2	0	0	4.2	5.7
Longitudinally extensive ON, %	95	NA	30	80	NA	NA	48.6	63

640 \* Only men included \*\*clinical involvement.  
 641 AE= affected eyes, ON: optic neuritis

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649 **Table 2 : Comparison of MRI Characteristics of MOGAD, AQP4 NMOSD and MS.**

<u>ON</u>	<u>MOGAD</u>	<u>AQP4 NMOSD</u>	<u>MS</u>
Bilateral	Frequent	Infrequent	Very rare
Lesion length	Long	Long	Short
OPN	Very frequent	Infrequent	Rare
Optic nerve head edema	Frequent	Infrequent	Infrequent, mild if present
Optic chiasm/ optic tracts	Rare	Frequent	Rare
Most frequently associated brain lesions	Normal/ nonspecific hyperintensities	Normal/ nonspecific hyperintensities	Typical MS lesions
<b><u>Spinal cord</u></b>			
Multiple lesions	Frequent	Rare	Frequent
LETM	Frequent	Frequent	Rare
Gadolinium enhancement	Infrequent	Frequent	Frequent
Conus	Frequent	Infrequent	Rare
H sign	Frequent	Infrequent	Rare
Evolution	Resolution	Atrophy	New lesions
<b><u>Brain</u></b>			
Lesions number	Few	Few	Numerous
Lesions morphology	Fluffy	Fluffy	Well delimited
Location	White matter Cortical (Rare)	Peri-aqueductal, hypothalamic, area postrema	Peri-ventricular (Dawson's fingers) Juxta-cortical/cortical
Evolution	Resolution	Resolution	Black Holes

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ON: optic neuritis, MOGAD: myelin oligodendrocyte glycoprotein associated disease; AQP4-NMOSD: aquaporin-4 neuromyelitis optica spectrum disorder, MS: multiple sclerosis, LETM: longitudinally extensive transverse myelitis

### **Figure 1: Optic neuritis in MOGAD patients**

- A-C: T1 weighted(T1W), IV+ sequence showing left ON with an important perineuritis (A,B, arrows) with papillary oedema on T2 Fluid-attenuated inversion recovery (FLAIR) sequence (C, arrow).
- D-F: Bilateral optic neuritis with an extensive optic nerves gadolinium enhancement (D,E) and associated T2 hyperintensity(F).

### **Figure 2: Spinal cord lesions in MOGAD patients**

- A1-3: Longitudinally extensive cord lesion with sagittal linear T2 hyperintensity (A.1) without gadolinium enhancement on T1W sequence(A.2), H sign on the T2W axial image (A3, arrow).
- B1-2: T2 hyperintensity(B.1, arrow) and gadolinium enhancement on T1W image(B.2, arrow) in a patient with a short dorsal myelitis.
- C: Spinal cord sagittal images showing T2W hyperintense short lesions within lower lumbar region in an asymptomatic patient.

### **Figure 3 : Brain MRI characteristic lesions in MOGAD patients**

- A-D: A patient with T2-FLAIR hyperintense lesion(A) in the right lentiform nucleus and in the left capsulo-thalamic region. The left lesion has a central, cloudy gadolinium enhancement (B), without apparent diffusion coefficient (ADC) restriction (C). A complete resolution of the abnormalities on the control T2-FLAIR sequence (D).
- E-H: Bilateral peri ventricular T2-FLAIR hyperintensity(E) without signal abnormality on DWI sequence (F). T2weighted (T2W) sagittal sequence showing associated cervical myelitis (G, arrow)). Pontine lesions disappeared on the control T2-FLAIR sequence (H).
- I-L: A patient with pseudo-tumorous frontal lesion: hyperintense on T2-FLAIR sequence(I) with a discrete central gadolinium enhancement (J), without ADC restriction(K). Axial T2-FLAIR from the control MRI shows an almost complete resolution of the lesion (L).

### **Figure 4: T2W lesions in MOGAD patients**

- A-C: Non-specific, juxtacortical (A,C arrows) and distal white matter (B) T2-FLAIR hyperintensities in patients with MOG-ON.
- D-G: MS-like pattern with well delimited white matter T2-FLAIR hyperintensities (D, E arrow) and a black hole on T1W sequence (F, arrow). Short ON sequelae on T2W axial image (G, arrow).

**Figure 5: Comparison of characteristic MRI findings between MOGAD, AQP4-NMOSD and MS.**

- A,E,I: T1W FAT saturated IV+ axial images with extensive left anterior ON accompanied with an important perineuritis (A, arrow) in a MOGAD patient. Bilateral lesions of the posterior part of the optic nerves/chiasm in AQP4-NMOSD (E, arrow) and a short left optic neuritis in a MS patient(I).
- T2W Sagittal (B,F,J) and axial (C,G,K) spinal cord images. MOGAD associated myelitis with a longitudinally extensive T2-hyperintense line (B, arrow). On axial sequence, the T2 hyperintensity is highly restricted to the gray matter forming an “H sign” (C, arrow). Longitudinally extensive cervical AQP4-NMOSD myelitis accompanied with an important cord swelling(F) and bright spotty lesion (G, arrow) on axial sequence. A patient with MS has multiple short T2-hyperintense lesions (J); on axial sequence, the lesion is located in the periphery of the cord in the left dorsal column(K).
- T2-FLAIR sequence shows: fluffy large and bilateral lesions in pons and cerebellar peduncles, adjacent to the fourth ventricle in a MOGAD patient(D); hypothalamic(H, arrowhead) and area postrema (H, arrow) signal abnormalities in AQP4-NMOSD patient and typical, multiple well delimited lesions in MS patient(L).









