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### ► To cite this version:

Françoise Durand-Dubief, Natalia Shor, Bertrand Audoin, Bertrand Bourre, Mickael Cohenf, et al.. MRI management of NMOSD and MOGAD: Proposals from the French Expert Group NOMADMUS. *Journal de Neuroradiologie / Journal of Neuroradiology*, 2025, 52 (1), pp.101235. 10.1016/j.neurad.2024.101235 . hal-04877409

**HAL Id: hal-04877409**

**<https://hal.science/hal-04877409v1>**

Submitted on 9 Jan 2025

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Original Article

## MRI management of NMOSD and MOGAD: Proposals from the French Expert Group NOMADMUS

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### ARTICLE INFO

#### Article History:

Available online 1 December 2024

#### Keywords:

MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease

### ABSTRACT

**Background:** Currently, there are no available recommendations or guidelines on how to perform MRI monitoring in the management of neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). The issue is to determine a valuable MRI monitoring protocol to be applied in the management of NMOSD and MOGAD, as previously proposed for the monitoring of multiple sclerosis.

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NMOSD, neuromyelitis optica spectrum disorder  
 MRI, magnetic resonance imaging  
 Recommendations  
 Disease management

**Objectives:** The objectives of this work are to establish proposals for a standardized and feasible MRI acquisition protocol, and to propose control time points for systematic MRI monitoring in the management of NMOSD and MOGAD.

**Methods:** A steering committee composed of 7 neurologists and 5 neuroradiologists, experts in NMOSD and MOGAD from the French group NOMADMUS, defined 8 proposals based on their expertise and a review from the literature. These proposals were then submitted to a Rating Group composed of French NMOSD / MOGAD experts.

**Results:** In the management of NMOSD and MOGAD, a consensus has been reached to perform systematic MRI of the brain, optic nerve and spinal cord, including cauda equina nerve roots, at the time of diagnosis, both without and after gadolinium administration. Moreover, it has been agreed to perform a systematic MRI scan 6 months after diagnosis, focusing on the area of interest, both without and after gadolinium administration. For long-term follow-up of NMOSD and MOGAD, and in the absence of clinical activity, it has been agreed to perform gadolinium-free MRI of the brain (+/- optic nerves) and spinal cord, every 36 months. Ideally, these MRI scans should be performed on the same MRI system, preferably a 3T MRI system for brain and optic nerve MRI, and at least a 1.5T MRI system for spinal cord MRI.

**Conclusions:** This expert consensus approach provides physicians with proposals for the MRI management of NMOSD and MOGAD.

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## Introduction

Neuromyelitis optica spectrum disorder (NMOSD) and the more recently identified myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) are both inflammatory demyelinating diseases of the central nervous system (CNS), distinct from multiple sclerosis (MS). Their clinical MRI phenotypes have been specified to consist more commonly in optic neuritis and/or longitudinal extensive transverse myelitis. Additional manifestations have been described for both diseases. Diagnosis criteria for NMOSD were defined by Wingerchuk et al in 2006, and in 2015, a new nomenclature defined the unifying term NMO spectrum disorders (NMOSD), with or without AQP4-IgG, based on essential clinical characteristics or MRI findings related to the optic nerve, spinal cord, area postrema, or other brainstem, diencephalic, or cerebral presentations.<sup>1-3</sup> MOGAD has been recently defined according to the diagnostic criteria of Banwell and collaborators in 2023.<sup>4</sup> MRI is now an essential component to achieve the positive diagnostic criteria for NMOSD or MOGAD, as well as to exclude other diagnoses, such as MS or other inflammatory diseases. MRI should also have a pivotal position in the monitoring of NMOSD and MOGAD to detect disease activity and assess potential serious adverse events associated with disease-modifying treatments.

Although the clinical and radiological course of these diseases is becoming better understood, there are currently few recommendations or consensus on the use of a harmonized MRI protocol for standardized diagnosis and follow-up in the management of NMOSD and MOGAD.

In the present paper, a working group of expert neurologists and neuroradiologists proposes a common, harmonized protocol for MRI acquisitions to be carried out during the diagnosis of NMOSD and MOGAD, as well as recommendations on the required milestones to perform systematic MRI follow-up of these diseases.

## Material and methods

The following proposals, based on a literature review and experts' opinion, have been established by consensus among the physicians and neuroradiologists of the NOMADMUS Expert Group (Appendix). First, a steering committee, composed of seven neurologists and five neuroradiologists practicing in expert centers in France, defined 8 proposals, based on a systematic analysis of the literature. Due to the limited amount of data in the literature on this topic, the level of scientific evidence for the proposals has been rated at level C (low level of evidence). The steering committee then submitted its proposals to a Rating

Group, composed of 23 French MS experts, none of whom had participated in the initial drafting. Each rater had to decide on her/his level of agreement for each proposal, and assign a score between 1 (fully disagree) and 10 (fully agree). After 2 rounds of rating, proposals were then classified as 'appropriate' if the median score was  $\geq 7$ , 'with strong agreement' if the range of rating was  $\geq 7$  and 'with relative agreement' if the minimal score is 2 raters disagreed and justified their position, even if the median score was  $\geq 7$ .

## Results

Detailed results of the ratings for all proposals are provided in Table 1.

**1 - In the management of NMOSD and MOGAD, at the time of the first episode, i.e. at the time of diagnosis, it has been proposed to perform MRI of the brain, optic nerve, and spinal cord, both without and after gadolinium administration.**

*In NMOSD management, it has been recommended that the diagnosis be accompanied by an exploration of the entire CNS. Optic neuritis is clinically severe and often simultaneous with visual field changes related to chiasmatic involvement. The MRI phenotype consists of an often extensive, bilateral, posterior optic neuritis, sometimes extending into the optic chiasm<sup>5,6</sup> (Fig. 1: A, B).*

*NMOSD also includes episodes of longitudinal extensive myelitis (LETM).<sup>6,7</sup> Some MRI aspects of LETM are highly suggestive of NMOSD: gray matter involvement, spinal cord edema, T1 hyposignal prior to injection and gadolinium enhancement, often extending to the brainstem,<sup>3</sup> or "bright spotty lesions" on T2-weighted images<sup>8-11</sup> (Fig. 1: C, D, E). Nevertheless, 7-14% of initial spinal cord injuries may not meet LETM criteria.<sup>3</sup> Short-segment transverse myelitis lesions have also been reported in NMOSD, sometimes isolated, and should therefore not exclude the diagnosis of NMOSD.<sup>12</sup>*

*Encephalic, diencephalic, brainstem and area postrema involvement has been described in cases of NMOSD<sup>2,10,11</sup> (Fig. 1: F, G, H). NMOSD patients may present with brain lesions, some of which may have an appearance compatible with MS lesions.<sup>3,13,14</sup> The latest consensus on diagnostic criteria for NMOSD, taking into account clinical and MRI aspects mentioned above, was published in 2015.<sup>3</sup> More recently, the Neuromyelitis Optica Study Group (NEMOS) has published updated recommendations for the diagnosis and differential diagnosis.<sup>6</sup> In addition, Latin American consensus recommendations for the management of NMOSD have suggested to perform brain, optic nerve and spinal cord MRI at the time of diagnosis.<sup>15</sup> Thus, considering the potential involvement of any part of the CNS, NMOSD experts recommend to perform a complete evaluation of the entire CNS.*

**Table 1**  
Detailed results of the rating for each proposal.

Proposals	Distribution of scores on rating scale 1–10										Median					
	1	2	3	4	5	6	7	8	9	10						
1	In the management of NMOSD and MOGAD, at the time of the first episode, i.e. at the time of diagnosis, it is proposed to perform brain, optic nerve, and spinal cord MRI, without and after gadolinium administration.										2	15	10			
2	In the management of NMOSD and MOGAD, in case of a new relapse, it is proposed to perform at least an MRI centered on the presumed area to be affected, or ideally brain, optic nerve, and spinal cord MRI, without and after gadolinium administration.										2	1	14	10		
3	In the management of NMOSD and MOGAD, it is suggested that MRI of the brain and optic nerve should preferably be performed on a 3T MRI scanner, ideally using the same MRI equipment and in a single examination.											3	14	10		
4	In the management of NMOSD and MOGAD, it is proposed to perform a brain /optic nerve MRI assessment following a standardized MRI acquisition protocol: <ul style="list-style-type: none"> <li>• Brain MRI:</li> <li>• 3D unenhanced T1 GE (1mm, gap 0, isotropic voxel), acquisition in the sagittal plane to include at least C3, if possible to C5-C6</li> <li>• Axial DWI with a b value at 1000</li> <li>• Gadolinium administration (0.1 mmol/kg)</li> <li>• 3D FLAIR Fat Sat (1mm, gap 0, isotropic voxel), acquisition in the sagittal plane (reconstruction plane on the optic nerves)</li> <li>• 3D gadolinium-enhanced T1 ES Fat Sat (1mm, gap 0, isotropic voxel), acquisition in the coronal plane if possible, otherwise sagittal</li> <li>• Optional: 3D DIR</li> <li>• Susceptibility weighted imaging</li> <li>• MRI of the optic nerves:</li> <li>• Coronal T2 or T2 DIXON or STIR (2mm, gap 0, voxel ≤ 0.6 mm)</li> <li>• Optional: gadolinium-enhanced T1 SE Fat Sat (2mm) acquisition in the coronal plane (if quality of 3D on the brain is not sufficient).</li> </ul>										1	4	2	10	10	
5	In the management of NMOSD and MOGAD, it is proposed to perform the spinal cord MRI on a 1.5 or 3T MRI scanner, ideally with the same MRI equipment and in 2 or 3 "steps": cervical, dorsal, and lumbar depending on the size of the patient, and including the cauda equina roots.										3	2	12	10		
6	In the management of NMOSD and MOGAD, it is proposed to perform a spinal cord MRI assessment following a standardized MRI acquisition protocol: 1. Spinal cord MRI: 1. Sagittal T2 (resolution between 2.5 mm and max 3 mm) 2. + one of the following sequences depending on local habits and optimization of the MRI system: 1. Sagittal Short Tau-Inversion Recovery (STIR) (resolution between 2.5 mm and max 3 mm) 2. Phase-Sensitive Inversion Recovery (PSIR), SPectral Attenuated Inversion Recovery (SPAIR) 3. MP2RAGE 4. FLuid And White matter Suppression (FLAWS) 5. WM-Nulling 3. Gadolinium administration (0.1 mmol/kg) 4. If lesion, axial T2 EG sequence on the main lesion 5. Sagittal gadolinium-enhanced T1 (resolution between 2.5 mm and max 3 mm).										1		3	3	10	10
7	In the management of NMOSD and MOGAD, it is proposed to perform a systematic follow up of the MRI at 6 months after the first clinical episode or after a relapse, centered on the affected area (brain ± optical nerves or spinal cord), without and after gadolinium administration.										1	3	2	10	10	
8	In the management of NMOSD and MOGAD, in the long-term follow-up without any relapse, it is proposed to perform a systematic control of the MRI every 36 months, brain (+/- optic nerves) and spinal cord MRI, without gadolinium.										1	1	5	1	9	10

In MOGAD management, it is also recommended to perform, at the time of diagnosis, an exploration of the entire CNS, as proposed by the recently published international MOGAD Panel.<sup>4,16,17</sup>

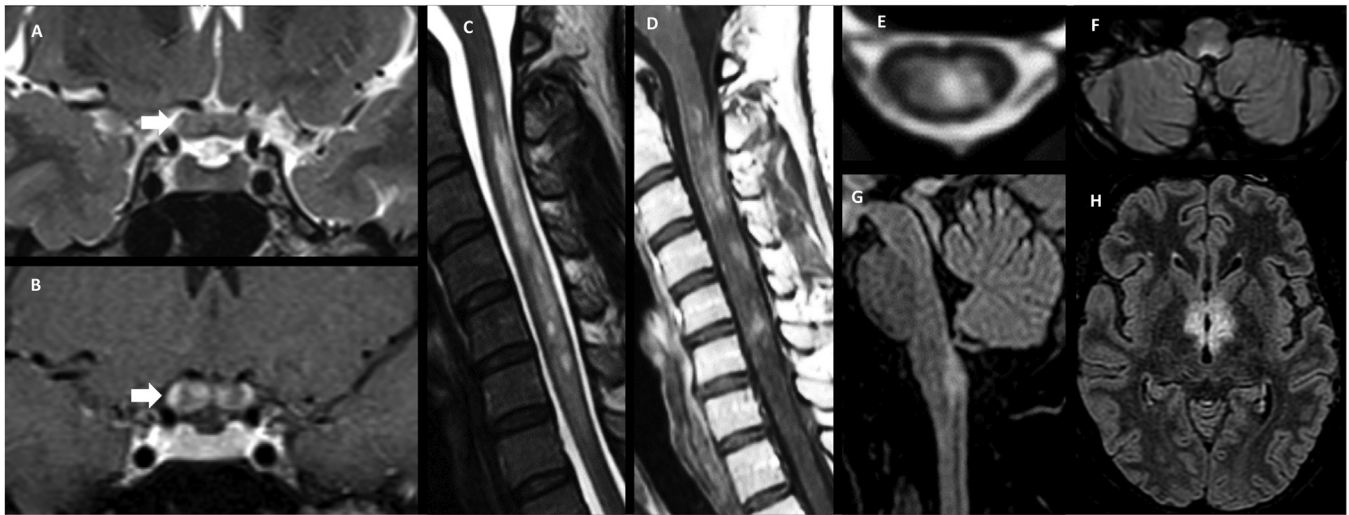
In MOGAD, optic nerve involvement is very common.<sup>18,19</sup> Optic neuritis is usually extensive (more than 50% of the optic nerve length), bilateral, and anterior<sup>5,20,21</sup> (Fig. 2: A). There is very often co-existing edema of the affected optic nerve head<sup>20,22</sup> and sometimes gadolinium enhancement of the optic nerve perineurium<sup>23</sup> (Fig. 2: B, C). These MRI characteristics of optic neuritis are also part of the recent MOGAD diagnostic criteria.<sup>4</sup>

Spinal cord involvement is also very common. LETM is the most common spinal cord abnormality visible on MRI<sup>24–27</sup> (Fig. 2: D). It is often located in the cervico-thoracic region, but an involvement of the caudal

part of the cord is classic.<sup>25,26,28</sup> A suggestive MRI aspect is the "H sign" visible on axial sequences, preferentially reflecting gray matter involvement<sup>20,25,28</sup> (Fig. 2: E). Pseudodilatation or marked T2 hyperintensity of the ependymal canal have been reported, and a linear enhancement of the ependymal canal (pencil-thin enhancement) can also be observed<sup>29,30</sup> (Fig. 2: D). Short myelitis has also been described.<sup>26</sup> Enhancement of acute lesion has been observed in 50% of cases, and leptomeningeal enhancement has also been reported<sup>25,31,32</sup> (Fig. 2: F). Finally, longitudinally extensive myelitis, central cord lesion or H-sign and conus lesion are now part of the recent diagnostic criteria of MOGAD.<sup>4</sup>

Brain MRI is most often normal in MOGAD.<sup>26</sup> Nevertheless, brain involvement is more common in MOGAD than in NMOSD.<sup>33</sup> Lesions,



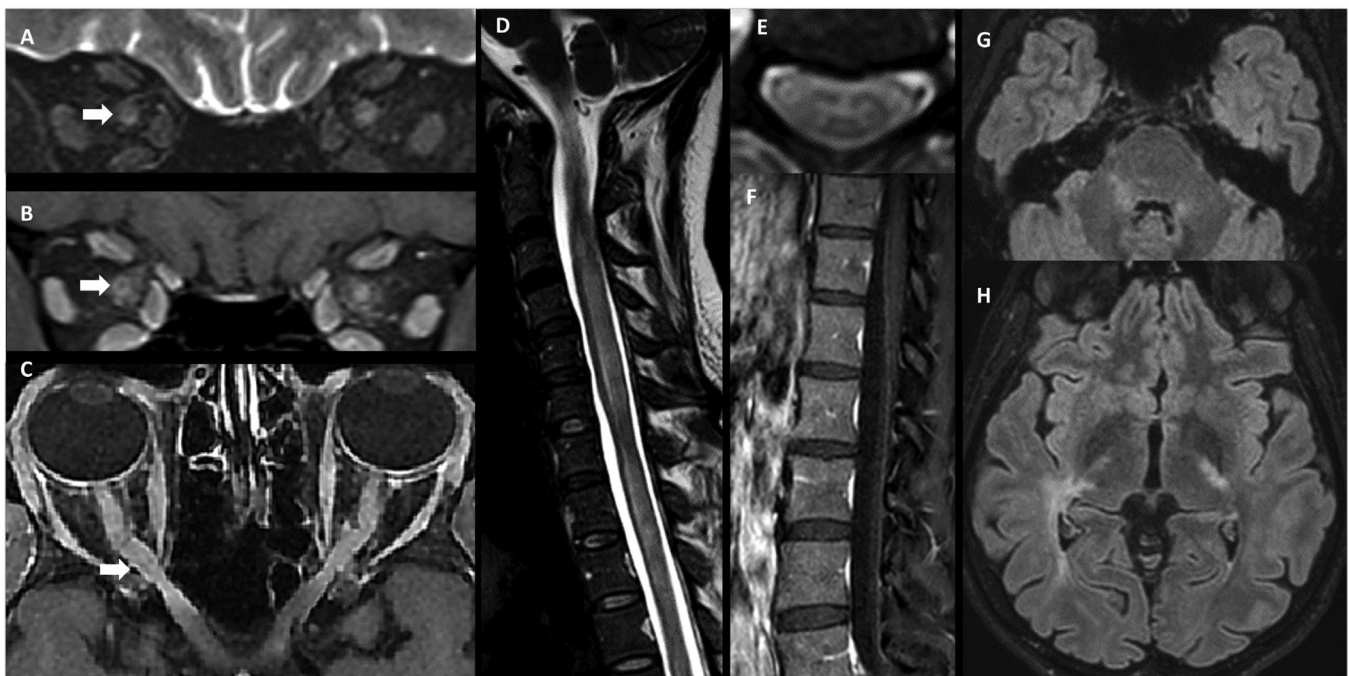


**Fig. 1.** Radiological features of NMOSD: A, B: Extensive, bilateral, posterior optic neuritis extending into the optic chiasm with chiasm edema (A) and gadolinium enhancement (B); C,D: Longitudinal extensive myelitis with spinal cord « edema » (C) and gadolinium enhancement (D); E: Aspect of "bright spotty lesions" on T2 weighted images; F, G: Area post-rema involvement; H: Hypothalamic involvement.

when present, are aspecific, taking on a "fluffy" appearance, or may have an MS-like inflammatory appearance<sup>20,34,35</sup> (Fig. 2: G, H). Involvement of the corpus callosum has been described as a longitudinally extensive T2-hyperintense lesion involving part or all of the corpus callosum.<sup>36</sup> Lesions appear to be more frequent in the brainstem and/or in the deep white matter<sup>16,24,25,37</sup> (Fig. 2: G, H). Enhancement is common in MOGAD cerebral lesions, which frequently have a non-specific patchy appearance. Leptomeningeal enhancement is more suggestive of MOGAD than NMOSD.<sup>38</sup> There may also be a presentation with focal cortical involvement, described as radiological encephalitis, which, when associated with epilepsy, has been termed FLAMES for "FLAIR Hyperintense cortical Lesions in MOG associated Encephalitis with Seizures"<sup>39-42</sup> or described as cerebral cortical encephalitis.<sup>43</sup> Multiple ill-defined T2 hyperintense

lesions in supratentorial and often infratentorial white matter, deep grey matter involvement have been described as part of the diagnosis of Acute Disseminated Encephalomyelitis (ADEM). All of these lesions are now part of the diagnostic MOGAD criteria.<sup>3</sup> Moreover, radiologic lag has been described as common within MOGAD attacks.<sup>44</sup> Indeed, dynamic imaging with frequent appearance and occasional disappearance of lesions within a single attack would suggest MOGAD diagnosis over MS and AQP4+NMOSD. Thus, as for NMOSD, the experts recommend to perform a complete evaluation of the CNS at the time of diagnosis in MOGAD management (Fig. 5).

However, the initial MRI examination is frequently conducted as an emergency or semi-emergency procedure prior to the diagnosis of NMOSD or MOGAD. This initial MRI scan may be incomplete in terms of



**Fig. 2.** Radiological features of MOGAD: A: Optic neuritis extensive, bilateral, and anterior as an hyperintensity on coronal T2 fat sat sequence; B, C: Gadolinium enhancement of the optic nerve perineurium in the coronal T1 fat sat sequence (B) and in axial T1 fat sat sequence (C); D: Longitudinal extensive myelitis often located in cervico-thoracic cord with aspect of pseudodilatation or marked T2 hyperintensity of the ependymal canal; E: Aspect of "H sign" visible on axial T2 GE sequence; F: Perimedullary or cauda equina roots leptomeningeal enhancement; G, H: Brain involvement corresponds to lesions with a "fluffy" appearance, and more often in the brainstem and/or in the deep white matter.

the region explored and/or the sequences performed. In such cases, it is advisable to perform additional MRI scans of the entire CNS as soon as possible after the onset of symptoms. This should provide an initial assessment of the structures involved, and a characterization of the lesions to guide diagnosis and management. The use of specific MRI sequences of the CNS, and in particular the order in which these are performed, should depend on the initial clinical presentation.

**2 - In the management of NMOSD and MOGAD, in case of a new relapse, it has been proposed to perform at least an MRI scan centered on the affected area, or ideally an MRI of the brain, optic nerve, and spinal cord MRI, both without and after gadolinium administration.**

In the case of a clinical relapse of NMOSD or MOGAD, it has been proposed to perform at least one MRI scan centered on the suspected area both without and after gadolinium administration. However, the problems are the same as for diagnosis. Encephalic damage, including damage to the optic nerves and/or spinal cord lesions may occur. It has therefore been suggested that the brain, optic nerve and spinal cord should ideally be examined, both without and after gadolinium administration. NEMOS has recently recommended to perform an MRI of the brain and spinal cord after any acute attacks<sup>45</sup> (Fig. 5).

**3 - In the management of NMOSD and MOGAD, it has been suggested that MRI of the brain and optic nerve should be performed on at least a 1.5T MRI scanner, but preferably on a 3T MRI scanner, ideally in a single examination and using the same scanner machine.**

In the literature, there is no recommendation on the minimum magnetic field strength to be used during MRI exploration of the brain and optic nerve in NMOSD and MOGAD, except in pediatric MOGAD.<sup>17</sup> In the latter publication, it was recommended to perform the brain and optic nerve MRI protocol in a single examination, using at least a 1.5T system and preferably a 3T system.<sup>17</sup> As in MS management, acquisitions on 3T MRI scanners enable better detection of demyelinating lesions and shorter acquisition times than on 1.5T MRI scanners.<sup>46</sup> Thus, similar to MS and pediatric MOGAD management, and in the absence of available recommendations in NMOSD and MOGAD, it has been proposed to perform brain /optic nerve MRI in a single examination and on a 3T MRI scanner, if this does not delay medical care.

However, the question is whether MRI of the encephalic/optic nerve and MRI of the spinal cord should be performed at the same time. This would enable immediate and complete exploration of the CNS, which is of particular interest at the time of diagnosis, and would reduce the number of gadolinium injections required, which is interesting given the risk of potential gadolinium accumulation in the CNS. Therefore, if encephalic/optic nerve and spinal cord MRI can be performed in a single session, the magnetic field strength should not be preferred and, depending on the availability, the MRI examination should be carried out at least 1.5T. If encephalic/optic nerve and spinal cord MRI should be performed in separate sessions for administrative or machine access reasons, or because there is no need to inject gadolinium, brain/optic nerve and spinal cord MRI should be performed in two separate stages: brain and optic nerve MRI should be performed on a 3T MRI system and spinal cord MRI on a 1.5T system. The aim is to obtain high quality images using sequences optimised for the study of these rare syndromes.

Otherwise, it has been recommended that MRI follow-up be performed on the same machine to facilitate image comparison, enable better detection of inflammatory activity and assess treatment efficacy.

**4 - In the management of NMOSD and MOGAD, it has been proposed to perform MRI assessment of the brain /optic nerve following a standardized MRI acquisition protocol:**

- **Brain MRI:**
  - **3D unenhanced T1-weighted gradient echo (GE) (1mm, gap of 0, isotropic voxel), acquisition in the sagittal plane to include at least C3, if possible up to C5-C6 (Time ~ 4–5 mn)**

- **Axial Diffusion-Weighted Imaging (DWI) with a b-value of at 1000 s/mm<sup>2</sup> (Time ~ 1 mn)**
  - **Gadolinium administration (0.1 mmol/kg)**
  - **3D Fluid-Attenuated Inversion Recovery (FLAIR) with fat saturation (Fat Sat) (1mm, gap of 0, isotropic voxel), acquisition in the sagittal plane (reconstruction plane on the optic nerves) (Time ~ 5 mn)**
  - **3D gadolinium-enhanced T1-weighted spin echo (SE) with fat saturation (Fat Sat) (1mm, gap of 0, isotropic voxel) acquisition in the sagittal plane (Time ~ 4 mn)**
  - **Optional: 3D Double Inversion Recovery (DIR) (Time ~ 6 mn)**
  - **Susceptibility weighted imaging (for MRI diagnosis only) (Time ~ 7 mn)**
- MRI of the optic nerves:
    - **Coronal T2 or T2 DIXON or Short Tau Inversion Recovery (STIR) ( $\leq 3$  mm, gap of 0, voxel  $\leq 0.6$  mm) (Time ~ 3.5 mn)**
    - **Optional: gadolinium-enhanced T1-weighted spin echo (SE) with fat saturation (Fat Sat) (2mm) acquisition in the coronal plane (if quality of 3D on the brain is not sufficient) (Time ~ 3.5 mn) (Fig. 3).**

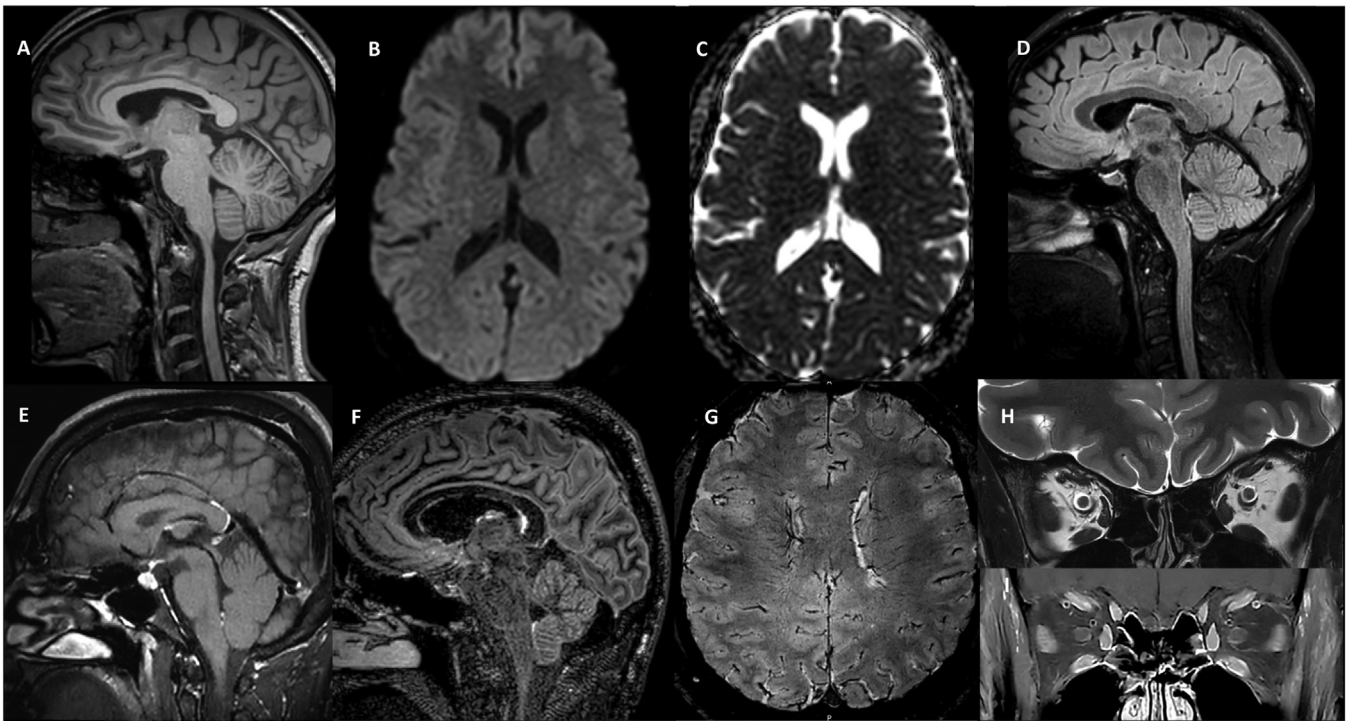
Consensus recommendations for a standardized brain MRI protocol have already been formulated for the management of NMOSD in Latin America.<sup>15</sup> However, there is no recommendation or consensus in the literature on a harmonized MRI acquisition protocol to be performed in MOGAD. Additionally, Cacciaguerra et al. have suggested MRI protocol for the diagnosis of NMOSD based on a protocol modified from MAGNIMS-CMSC-NAIMS consensus recommendations according to authors' personal experience.<sup>47</sup> Nevertheless, as in the management of MS, it has been proposed and recommended to use a standardized brain and spinal cord MRI protocol.<sup>48,49</sup>

The proposed protocol is based on that recommended for MS, especially since the exact diagnosis is not known at the time of the first MRI. Depending on the symptomatology, and if the suspected pathology is indeed NMOSD or MOGAD, the protocol may be supplemented. As in MS management, 3D T1 or 3D FLAIR acquisitions should now be preferred to 2D acquisitions as they have been reported to allow better detection of inflammatory lesions and better visualization and detection of lesions in all 3 planes after reconstruction.<sup>48,50–52</sup> This improved visualization enabled with 3D acquisitions can be applied to NMOSD and MOGAD lesions. The sagittal acquisition plane for 3D T1 and 3D FLAIR sequences should be preferred due to the minimal number of slices to be acquired and, therefore reduced machine time. Furthermore, the sagittal acquisition allows exploration of the upper part of the spinal cord. In addition, 3D FLAIR sequences have been reported to be superior to 2D in detecting lesions in the postrema area in NMOSD, beyond the detection of T2 brain lesions.<sup>53</sup> 3D acquisitions sequences have also been recommended by the European Pediatric Neurology Society in MOGAD and by the Latin American consensus recommendations.<sup>15,17</sup> In patients with optic neuritis, the 3D FLAIR sequence has been validated to identify hypersignal intensity of the optic nerve head corresponding to optic nerve head edema, which is a useful feature in MOGAD diagnosis.<sup>54</sup>

Following the recommendations of the French Observatory of Multiple Sclerosis (OFSEP) protocol in MS, and for its application in NMOSD and MOGAD, a 3D gradient echo T1 sequence has been proposed for the evaluation and the automatic processing of the gadolinium-enhanced T1-weighted lesion load.<sup>48</sup> Measurements of cerebral atrophy and possibly the cervical spinal cord may also be carried out if they prove to be of interest in NMOSD and MOGAD management in the future.

Diffusion-weighted imaging (DWI) sequences can highlight acute lesions that may show diffusion restriction and, in some cases, a decrease in apparent diffusion coefficient (ADC) allowing cases of T2 shine-through to be eliminated. The hypothesis is that these lesions may correspond to highly active lesions with hypercellularity.<sup>55</sup> A work performed





**Fig. 3.** Brain /optic nerve MRI standardized MRI acquisition protocol A: 3D unenhanced T1-weighted gradient echo (GE) (1mm, gap of 0, isotropic voxel), acquisition in the sagittal plane to include at least C3, if possible to C5-C6; B, C: Axial Diffusion-Weighted Imaging (DWI) with a b-value at 1000 s/mm and axial ADC map; D: 3D Fluid-Attenuated Inversion Recovery (FLAIR) with fat saturation (Fat Sat) (1mm, gap of 0, isotropic voxel), acquisition in the sagittal plane (reconstruction plane on the optic nerves); E: 3D gadolinium-enhanced T1-weighted spin echo (SE) with fat saturation (Fat Sat) (1mm, gap of 0, isotropic voxel) acquisition in the sagittal plane; F: Optional: 3D Double Inversion Recovery (DIR), G: Susceptibility weighted imaging (MRI diagnosis only). MRI of the optic nerves: H: Coronal T2 or T2 DIXON or Short Tau Inversion Recovery (STIR) ( $\leq 3$  mm, gap of 0, voxel  $\leq 0.6$  mm); I: Optional: gadolinium-enhanced T1-weighted spin echo (SE) with fat saturation (Fat Sat) (2mm) acquisition in the coronal plane (if quality of 3D on the brain is not sufficient).

on tumefactive brain lesions comparing MS, AQP4+NMOSD and MOGAD, showed that the presence of peripheral T2-hypointense rim, T1-hypointensity, diffusion restriction (particularly an arc pattern), ring enhancement, and Baló-like or cystic appearance favored MS over MOGAD. MRI features were broadly similar in MOGAD and AQP4+NMOSD, except for more frequent diffusion restriction in AQP4+NMOSD than in MOGAD.<sup>56</sup> Thus, as proposed in the management of MS, DWI sequences may provide additional information on lesion characterization. However, they cannot replace gadolinium-enhanced T1-weighted sequences in the evaluation of inflammation.<sup>57</sup> In addition, DWI sequences may be of interest for monitoring the risk of complications that may arise with the use of new treatments in NMOSD and MOGAD management.

A gadolinium-enhanced T1-weighted SE sequence is advised for brain MRI diagnosis, or at the onset of a relapse in NMOSD<sup>11,15</sup> or in MOGAD.<sup>17</sup> The delay between gadolinium administration and the acquisition of such a sequence should be at least 5 min, as is the case in the management of MS. Gadolinium administration can be performed before the acquisition of a 3D FLAIR sequence, as it does not interfere with the evaluation of 3D FLAIR images and optimizes the 5-min waiting time.<sup>49,58</sup> A SE sequence should be preferred for gadolinium-enhanced T1-weighted acquisition due to its superior detection sensitivity to gadolinium enhancement compared to GE sequences.<sup>59,60</sup>

As in MS management, it has been recommended to limit the number of gadolinium injections for the follow-up of NMOSD or MOGAD patients, evidence of gadolinium deposition in the CNS, having led to recommendations on the iterative use of gadolinium in the management of MS.<sup>48,49,61</sup> Sequences with gadolinium administration should therefore not be systematically performed during MRI follow-up of NMOSD and MOGAD patients (cf. proposals 1, 7, 8). It should be noted that macrocyclic agents (gadoteridol, gadobutrol,

and gadoteric acid) have received European Medicines Agency approval.

It has also been proposed to perform magnetic susceptibility imaging to distinguish NMOSD and MOGAD from MS. Indeed, the central vein sign (CVS) is usually reported in MS lesions that develop around small veins.<sup>62,63</sup> CVS confers a sensitivity of 68.1% and a specificity of 82.9% for distinguishing MS from non-MS conditions using a threshold of 35% for the proportion of lesions with CVS.<sup>64</sup> The proportion of lesions with CVS was significantly higher, 80% versus 32%, in MS patients than in NMOSD patients. The authors have therefore considered that if more than 50% of the lesions on a given MRI showed CVS, the patient could be diagnosed with MS with 94% accuracy.<sup>65</sup> This concept has been echoed in recent publications.<sup>66,67</sup>

A standardized MRI acquisition protocol has also been proposed for optic nerve exploration, which is essential for obtaining comparable images and making it possible to accurately analyze the appearance and location of optic neuritis, to aid diagnosis and enable effective follow-up. As detailed in the initial proposal, NMOSD frequently causes optic neuropathies that are bilateral, typically severe, extensive, posterior and sometimes accompanied by chiasmatic involvement.<sup>5,6</sup> MOGAD also often leads to bilateral and extensive optic neuropathies, but these are generally anterior, extending up to the optic nerve head.<sup>5,20,21</sup> These suggestive radiological features help differentiate these optic neuropathies from those occurring in MS, which are often short, non-extensive, and unilateral. It is crucial to optimize the imaging protocol for optic nerves. However, it is also important to respect the practices of the various expert centers in this field, and to propose a harmonized protocol for non-specialized centers. It is therefore recommended to perform a T2-weighted or T2 Dixon sequence, preferably with coronal acquisition and a slice thickness of 3 mm or less. Other T2-weighted sequences have been proposed such as STIR, 2D coronal fast SE Fat Sat, 3D DIR or 3D FLAIR Fat Sat sequences.<sup>68,69</sup> Regarding these different T2-weighted sequences,

there is no data in the literature that favor one sequence over another. No comparative studies have been conducted to date. All these sequences are proposed because they are used in the various expert centers in France, depending on local practices. When gadolinium administration is required, a T1-weighted SE acquisition with fat saturation coronal slice orientation has been recommended, as proposed in other acquisition protocols.<sup>49,68</sup>

**5 - In the management of NMOSD and MOGAD, it has been proposed to perform spinal cord MRI on a 1.5T or 3T MRI scanner, ideally with the same MRI equipment and in 2 or 3 "steps" for the cervical, dorsal, and lumbar section depending on the size of the patient, and including the cauda equina roots.**

As in MS management, it has been recommended to perform spinal cord MRI on a 1.5T or 3T equipment.<sup>48,49</sup> Indeed, unlike brain MRI, the use of 3T MRI does not provide better detection of spinal cord lesions than 1.5T MRI.<sup>70</sup>

Thus, in the management of NMOSD and MOGAD, it has been proposed to perform MRI of the whole spinal cord in 2 or 3 "steps" for the cervical, dorsal, and lumbar section, depending on the size of the patient. As detailed in the argument of Proposition 1, NMOSD or MOGAD lesions can affect all sections of the spinal cord.

In the management of MOGAD, a special feature is to recommend exploration of the entire spinal cord, including the cauda equina roots. MOGAD may preferably involve the caudal part of the cord.<sup>25,71</sup> Other publications have described aspects of perineuritis, and the presence of gadolinium enhancement of the cauda equina roots. It has therefore been recommended to perform an MRI examination of the whole spinal cord, including cauda equina roots, after gadolinium administration.<sup>72</sup>

**6 - In the management of NMOSD and MOGAD, it has been proposed to perform spinal cord MRI following a standardized MRI acquisition protocol:**

**1. Spinal cord MRI:**

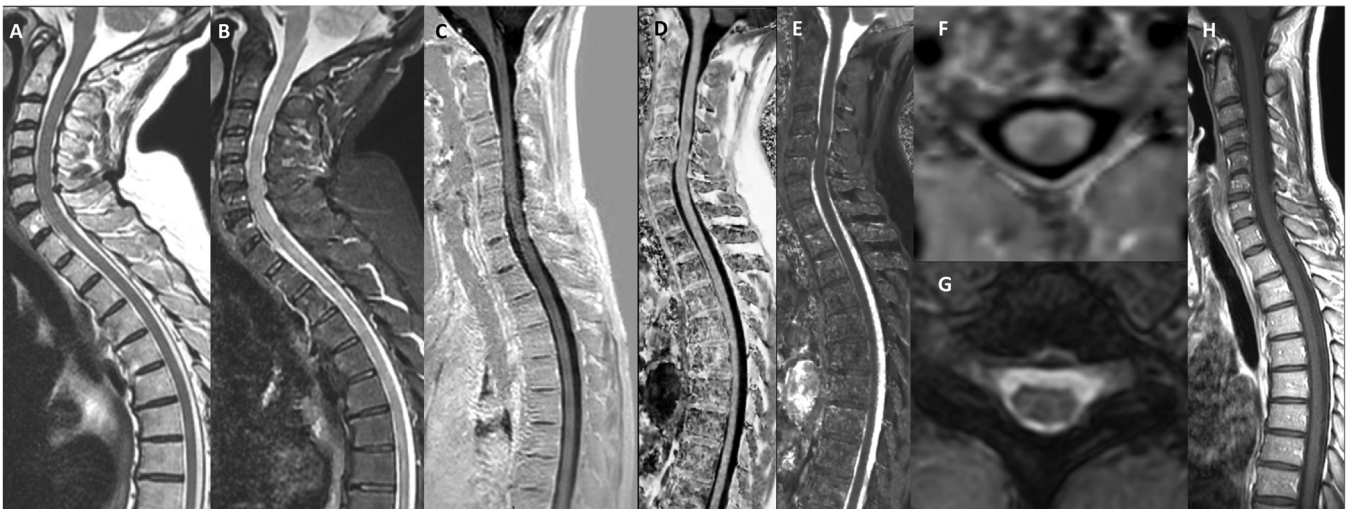
1. **Sagittal T2-weighted imaging (slice thickness between 2.5 mm and 3 mm) (Time ~ 3 mn/section)**
2. **+ one of the following sequences depending on local habits and optimization of the MRI system:**
  1. **Sagittal Short Tau-Inversion Recovery (STIR) (slice thickness between 2.5 mm and 3 mm) (Time ~ 4–5 mn/section)**
  2. **3D DIR (Time ~ 5–6.5 mn)**

3. **Phase-Sensitive Inversion Recovery (PSIR) (Time ~ 3.5–5 mn)**
4. **MP2-RAGE or FLuid And White matter Suppression (FLAWS) (Time ~ 3–5 mn/section) or White Matter-Nulling MP-RAGE (Time ~ 4.5 mn)**

3. **Gadolinium administration (0.1 mmol/kg)**
4. **If a lesion is present, axial T2 GE or T2 SE sequence centered on the main lesion**
5. **Sagittal gadolinium-enhanced T1-weighted imaging with or without fat saturation (slice thickness between 2.5 mm and 3 mm) (Time ~ 2.5 mn/section) (Fig. 4).**

To date, consensus recommendations for a standardized spinal cord MRI protocol have only been formulated for the management of NMOSD.<sup>15</sup> Additionally, Cacciaguerra et al. also have suggested spinal cord MRI protocol for the diagnosis of NMOSD based on a protocol modified from MAGNIMS-CMSC-NAIMS consensus recommendations according to authors' personal experience.<sup>47</sup> Moreover, there is no recommendation or consensus in the literature on a harmonized spinal cord MRI acquisition protocol to be performed in MOGAD. It has thus been proposed to use a standardized spinal cord MRI protocol,<sup>48,49</sup> including a sagittal T2-weighted sequence with a resolution between 2.5 mm and max 3 mm as in the OFSEP protocol for MS management.<sup>48</sup> This sequence has also been recommended by the European Pediatric Neurology Society in MOGAD.<sup>17</sup>

As in MS management, an additional sequence is also recommended since a T2-weighted sequence alone would be insufficient for the detection of MS lesions, and the same can be assumed for NMOSD and MOGAD.<sup>73,74</sup> Indeed, the Magnetic Resonance Imaging in MS group (MAGNIMS) recommended the use of a standardized MS follow-up protocol including at least 2 of the following 3 sequences: a T2-weighted sequence or a proton density-weighted sequence or a STIR sequence.<sup>49</sup> MAGNIMS has also proposed the use of a biplanar T2-weighted sequence.<sup>11</sup> Other studies have showed that at 3T, proton density and STIR sequences were more sensitive in detecting MS lesions in the cervical cord than T2-weighted sequences.<sup>75</sup> STIR is therefore one of the possible additional sequences to be carried out with a resolution of between 2.5 mm and a maximum of 3 mm.



**Fig. 4.** Spinal cord MRI protocol: A: Sagittal T2-weighted imaging (slice thickness resolution between 2.5 mm and max 3 mm) + one of the following sequences depending on local habits and optimization of the MRI system: B: Sagittal Short Tau-Inversion Recovery (STIR) (slice thickness resolution between 2.5 mm and max 3 mm); C: Sagittal Phase-Sensitive Inversion Recovery (PSIR) or, SPectral Attenuated Inversion Recovery (SPAIR); D, E, F: MP2-RAGE or FLuid And White matter Suppression (FLAWS) or White Matter-Nulling MP-RAGE (D : corrected-Real; E: T1 map; F: Axial Reformat); If a lesion is present : G: axial T2 GE sequence centered on the main lesion; H: Sagittal gadolinium-enhanced T1-weighted imaging (slice thickness resolution between 2.5 mm and max 3 mm).



Currently, several other sequences can be offered besides STIR. Indeed, STIR is a complete T2-weighted sequence. It differs from Spectral Presaturation with Inversion Recovery (SPIR) in several aspects. SPIR can be seen as a different type of magnetization preparation module that can be appended to other sequences. It selectively suppresses fat, can be used with sequences of any weighting and has higher signal-to-noise than STIR. Double inversion recovery (DIR) is another T2 based sequence in which CSF and white matter are nulled, which has been shown to improve detection of spinal cord lesions.<sup>76</sup>

The MP2-RAGE sequence, by comparison, uses GE readouts between each inversion pulse which results in a strongly T1-weighted image with superior gray matter (GM) to white matter (WM) contrast than available by MP-RAGE. FLAWS is a specific MP2RAGE with specific inversion times to null CSF and WM. WM nulled version of MP-RAGE with a single inversion time can also be used to null the WM,<sup>77</sup> resulting in high contrast between inflammatory lesions and WM. These sequences have been used in the brain, but preliminary data suggest that they could improve the sensitivity of detection of inflammatory lesions in the spinal cord.<sup>78</sup> Thus, for the management of NMOSD and MOGAD, and for the same reasons as for MS, it has been recommended to perform at least one of the following additional sequences: STIR, PSIR, MP2-RAGE, FLAWS, WM nulled MP-RAGE depending on local clinical practice and optimization of these MRI sequences.<sup>79,80</sup>

In the presence of one or more lesions, an axial T2-weighted GE or T2-weighted SE sequence should be systematically performed on the main lesion. Depending on local practice, an axial cumulative multi-echo GE sequence may also be performed and are particularly performant for the cervical spinal cord. Such a sequence makes it possible to specify the diagnosis according to the extension and location of signal hyperintensities. It is also useful for identifying the presence of bright spotty lesions suggestive of NMOSD AQP4+<sup>9,81</sup> or H sign suggestive of MOGAD.<sup>20,25,82</sup>

Gadolinium administration during spinal cord MRI is very important to identify LETM in the diagnosis of NMOSD or MOGAD, and to rule out a possible differential diagnosis (sarcoidosis, arteriovenous fistula, spinal cord ischemia, paraneoplastic myelopathy).<sup>83</sup> As with brain and optic nerve MRI, sequences performed with gadolinium administration should remain optional and depend on NMOSD and MOGAD evolution (cf Proposals 1, 7, 8). The sagittal T1 post-contrast sequence may be performed with or without fat saturation. The sequence with fat saturation may be preferred for better contrast visibility of the cauda equina roots.

**7 - In the management of NMOSD and MOGAD, it has been proposed to perform systematic MRI follow-up 6 months after the first clinical episode or after a relapse, centered on the affected area (brain ± optical nerves or spinal cord), both without and after gadolinium administration.**

There are no recommendations in the literature regarding the milestones at which MRI control should be performed in the setting of MOGAD and NMOSD monitoring. The objective of a systematic MRI control at 6 months is mainly to appreciate the lesion dynamics. It is

essential to check for an improvement or even the disappearance of the initial lesions. It is also essential to ensure that gadolinium enhancement has disappeared, in order to rule out another differential diagnosis in case of persistent gadolinium enhancement.

In NMOSD, complete resolution of T2 hyperintense spinal cord lesions is uncommon.<sup>28,84</sup> Bright spotty lesions are transient as they tend to disappear during MRI follow-up.<sup>9,81</sup> NMOSD LETM often evolves towards partial resolution of the spinal cord T2 hyperintensity, but also towards a cord atrophy appearance, or a residual T1 hypointensity in 9% of cases.<sup>85–88</sup> Sometimes there can be signs of myelomalacia.<sup>89</sup> NEMOS has recently recommended such repeated brain and spinal cord MRIs to reassure the diagnosis during the initial phase of the disease.<sup>45</sup>

Moreover, several studies have highlighted signs of subclinical MRI activity such as the appearance of silent lesions on a MRI scan performed during a relapse in NMOSD.<sup>90,91</sup> As silent lesions on MRI in remission NMOSD are rare, their presence has led to discussion of the imminent risk of relapse in NMOSD.<sup>92,93</sup> Similar observations have been made for spinal cord lesions in NMOSD.<sup>93,94</sup>

In MOGAD, enhancement is common with cerebral lesions that rarely persists beyond 3 months(38). In MOGAD, lesions demonstrate a great reduction in T2 lesion area, even a complete resolution of T2 hyperintense spinal cord lesions in about 62–79% of cases.<sup>28,31,84,88,95</sup> The median time from spinal cord lesion detection to MRI normalization has been reported as around 9 months in one study, but description can be only about several days.<sup>84,88</sup> There is almost no atrophy nor T1 hypointensity in MOGAD.<sup>85,88</sup> However, specific studies have identified a reduction of the gray matter volume in spinal cord exclusively in areas affected by previous attacks.<sup>85</sup> Thus, some groups have recommended to perform a follow-up MRI scan between 3 and 6 months after a first episode.<sup>17</sup>

In MOGAD, it has been highlighted that there were 33% and 3% of silent lesions on MRI performed during relapse and remission, respectively.<sup>93,96</sup> Thus, silent lesions are considered as rare in routine MRI follow-up, even more if located in the spinal cord.<sup>93,96</sup> As for NMOSD, the presence of silent lesions in MOGAD has led to discussion of an imminent risk of relapse.<sup>93</sup> Other studies have suggested that systematic MRI follow-up in MOGAD was of relatively low interest for the detection of asymptomatic brain lesions.<sup>84,93,96</sup>

For all of the aforementioned reasons, in the management of NMOSD and MOGAD, NOMADMUS experts have proposed to perform a systematic follow-up MRI scan 6 months after the first clinical episode or after a relapse, centered on the affected area (brain +/-optical nerves or spinal cord), both without and after gadolinium administration (Fig. 5).

**8- In the management of NMOSD and MOGAD, in the long-term follow-up without any relapse, it has been proposed to perform a MRI control every 36 months, brain (+/- optic nerves) and spinal cord MRI, without gadolinium.**

To our knowledge, there is no recommendation in the literature regarding the appropriate frequency for performing MRI in the monitoring of NMOSD and MOGAD. As previously stated in the argument

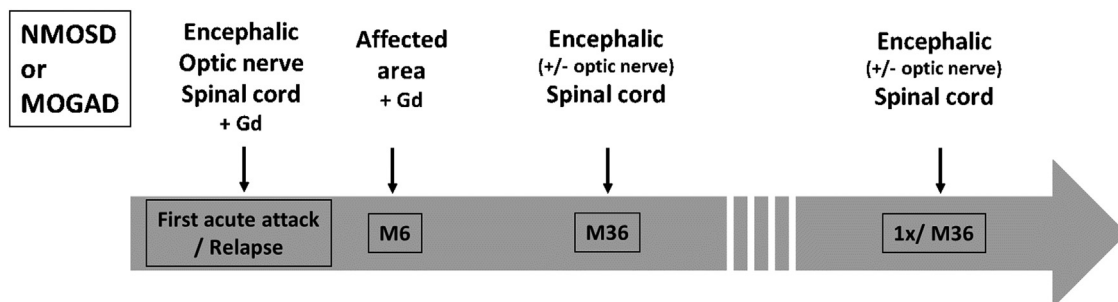


Fig. 5. Graphic representation of the proposals of the French Expert Group NOMADMUS on when and what type of MRI examination should be performed for the monitoring of NMOSD et MOGAD.

presented in Proposal 7, and due to the rarity and the irrelevance of silent lesions in NMOSD and MOGAD, studies have suggested that systematic MRI follow-up was of limited value in detecting disease activity. Therefore, some experts have suggested that systematic MRI follow-up should not be conducted.

It is important to note that the situation differs from that of MS, where there is a potential for infraclinical radiological inflammatory activity that may necessitate therapeutic adaptation. In the context of NMOSD and MOGAD, given the near absence of infraclinical activity, there is no requirement to propose a regular/annual MRI monitoring, which is the recommendation and practice in MS.

Nevertheless, even if knowledge about NMOSD and MOGAD has improved, these two syndromes remain rare, and it is likely that there are still aspects that are poorly understood. While studies have demonstrated little detection of silent lesions during MRI follow-up, others have reported the detection of a significant number, justifying "at least" a certain amount of vigilance, particularly in MOGAD which has been described more recently.<sup>93,96</sup> Thus, NEMOS recently recommended a brain and spinal cord MRI for safety surveillance.<sup>44</sup>

Furthermore, keeping minimal MRI follow-up seems important to ensure that there are no potential treatment-related complications. This is particularly true in the context of the therapeutic management of NMOSD, where treatment must be maintained for life, and sometimes in elderly patients. It is possible that long-term immunosuppressive therapies, may be associated with an increased risk of infectious complications. It is established that broad-spectrum immunosuppressive therapies or anti CD20 antibodies may elevate the risk of infection, including progressive multifocal leukoencephalopathy (PML). Although fatal cases of PML have been reported in rare instances following the administration of these therapies, patients should be monitored at regular intervals for the emergence or worsening of neurological symptoms or signs suggestive of PML, in addition to the clinical examination. Furthermore, new therapies dedicated to NMOSD, such as anti-complement or anti-IL-6 antibodies have specific tolerance profiles and require specific care. Particularly, monoclonal antibodies that binds to the complement protein C5 can cause serious infections, including among others meningococcal infections, despite meningococcal vaccination.<sup>97–100</sup> To prevent such infections, it is recommended that a strategy of complete meningococcal vaccination be implemented, with the additional measure of prophylactic antibiotic therapy pending the efficacy of this vaccination, should it be deemed necessary.<sup>45</sup> Also, data on the long-term use of anti-IL6 antibodies in NMOSD remain scarce and mainly arise from other indications. The observed side effects are more pronounced in areas outside the CNS. Thus far, anti-IL6 antibodies have demonstrated a favorable safety profile.<sup>45</sup> Currently, there have been no reported cases of PML associated with these therapies.

Additionally, MRI monitoring may prove beneficial for long-term monitoring of lesions affecting the brain and spinal cord. This could facilitate the identification of neurodegenerative phenomena, manifested as cerebral or spinal cord atrophy.<sup>86</sup> While measures of atrophy are not currently employed in individual clinical practice, the presence of atrophy may be a contributing factor in understanding the disability of certain patients with NMOSD or MOGAD.<sup>86</sup> However, it is important to acknowledge that the field of neurodegeneration in NMOSD and MOGAD is still evolving, with current literature providing inconclusive evidence. In NMOSD, there is still a lack of consensus regarding the understanding of lesional microstructural abnormalities, or normal-appearing WM abnormalities.<sup>47</sup> There is also a very limited amount of data available for MOGAD. Although a number of different markers of neurodegeneration can be employed in research using advanced non-conventional sequences, atrophy nevertheless represents an intriguing MRI marker for assessment.

NOMADMUS experts therefore suggest MRI every 36 months to ensure radiological stability, to check for the possible occurrence of silent

lesions on MRI, and monitor the absence of complications related to prolonged immunosuppression (Fig. 5). As for previous MRI scans, it is recommended that MRI follow-up be performed on the same machine, following the same protocol to facilitate comparison of high-quality images, to allow better detection of MRI inflammatory lesions and ensure treatment safety.

This work, conducted by the NOMADMUS study group, aims to provide physicians with some proposals for the MRI management of NMOSD and MOGAD.

### Declaration of competing interest

Françoise DURAND-DUBIEF has nothing to disclose.

Natalia SHOR has nothing to disclose.

Bertrand AUDOIN has nothing to disclose.

Bertrand BOURRE serves on scientific advisory board, has received funding for travel and honoraria from Alexion, Biogen, BMS, Horizon, Janssen, Merck, Novartis, Sanofi, Sandoz and Roche.

Mikael Cohen has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Biogen, Merck, Sanofi, Roche, Celgene-BMS, Janssen, Alexion, Horizon Therapeutics and Ad Scientiam.

Stéphane KREMER has nothing to disclose.

Elisabeth MAILLART reports research support from Biogen and personal fees for lectures and advisory boards from Alexion, Biogen, Horizon, Janssen, Merck, Novartis, Roche, Sanofi, and Teva.

Caroline PAPEIX has received personal compensation for consulting, serving on a scientific advisory board, speaking from Alexion, Horizon, Roche.

Aurélien RUET has received funding for travel or speaker or consultant honoraria from Biogen, Alexion, Novartis, Sanofi, Merck, Horizon Therapeutic; and received research support from Biogen, BMS, Sanofi, Roche, Merck.

Julien SAVATOVSKY has nothing to disclose.

Thomas TOURDIAS has nothing to disclose.

Xavier AYRIGNAC has received consulting fees and lecturing fees, travel grants and unconditional research support from Alexion, Biogen, Genzyme, Janssen, Merck Serono, Novartis, Roche, Sanofi Aventis and Teva Pharma.

Jonathan CIRON has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Biogen, Novartis, Merck, Sanofi, Roche, Alexion, Horizon Therapeutics, none related to this study.

Nicolas COLLONGUES has received honoraria for consulting or presentation from Alexion, Biogen Idec, Bristol-Myers Squibb, Horizon Therapeutics, Merck Serono, Novartis, Roche and Sanofi-Genzyme and is a member of the Editorial Board of the Journal de la Ligue Française contre la Sclérose en plaques and the Neurology and Therapy Journal.

David LAPLAUD served on scientific advisory boards for Alexion, BMS, Roche, Sanofi, Novartis, Merck, Janssen and Biogen, received conference travel support and/or speaker honoraria from Alexion, Novartis, Biogen, Roche, Sanofi, BMS and Merck and received research support from Fondation ARSEP, Fondation EDMUS and Agence Nationale de la Recherche.

Laure MICHEL has nothing to disclose.

Romain DESCHAMPS has received personal compensation for serving on a scientific advisory board or travel grants from Biogen, Roche, Alexion, and Novartis.

Eric THOUVENOT received consulting and lecturing fees, travel grants or unconditional research support from Actelion, Biogen, BMS, Merck, Novartis, Roche, Teva pharma.

Hélène ZEPHIR received consulting fees and invitation for congresses from Alexion, Horizon Therapeutics, Roche, Sanofi, Janssen, Biogen Idec, Merck, BMS. HZ received research supports from Novartis, Roche.

Romain MARIGNIER serves on scientific advisory boards for Horizon Therapeutics/Amgen; and has received funding for travel and fees from Alexion, Amgen Biogen, Roche, Sanofi.

François COTTON reports grants, consulting fees, and non-financial support from Biogen, Bracco imaging, Merck-Serono, Novartis, Philips and Roche.

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