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### ► To cite this version:

Sylvain Rabasté, Alvaro Cobo-Calvo, Veronica Nistiriuc-Muntean, Sandra Vukusic, Romain Marignier, et al.. Diagnostic value of bright spotty lesions on MRI after a first episode of acute myelopathy. American Journal of Neuroradiology, 2020, 10.1016/j.neurad.2020.04.006 . hal-02921544

**HAL Id: hal-02921544**

**<https://hal.science/hal-02921544>**

Submitted on 13 Feb 2023

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## DIAGNOSTIC VALUE OF BRIGHT SPOTTY LESIONS ON MRI AFTER A FIRST EPISODE OF ACUTE MYELOPATHY

### Authors

Sylvain Rabasté, MD<sup>1#</sup> and Alvaro Cobo-Calvo, MD, PhD<sup>2, 3#</sup>, Veronica Nistiriuc-Muntean, MD<sup>1</sup>, Sandra Vukusic, MD, PhD<sup>2, 3</sup>, Romain Marignier, MD, PhD<sup>2, 3</sup>, François Cotton, MD, PhD<sup>1, 4\*</sup>, On behalf of the OFSEP and NOMADMUS Study Group<sup>a</sup>

<sup>1</sup>Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, Service de Radiologie, Pierre-Bénite F-69310, France.

<sup>2</sup>Hospices Civils de Lyon, Hôpital Neurologique Pierre Wertheimer, Service de neurologie - sclérose en plaques, pathologies de la myéline et neuroinflammation, Centre de référence des maladies inflammatoires rares du cerveau et de la moelle – MIRCEM, Bron F-69500, France.

<sup>3</sup>Université Lyon-1, Centre de Recherche en Neurosciences de Lyon, INSERM U1028, CNRS UMR5292, Lyon F-69008, France.

<sup>4</sup>Université Lyon-1, CREATIS, INSERM U1044, CNRS UMR 5220, Villeurbanne F-69100, France.

# Contributed equally to this work.

\*Corresponding author : francois.cotton@chu-lyon.fr (F. Cotton).

**Disclosure of interest:** The authors declare that they have no competing interest.

<sup>a</sup> On behalf of the OFSEP and NOMADMUS Study Group :

AUDOIN Bertrand, Hôpital de La Timone, 13005, Marseille, bertrand.audoin@ap-hm.fr

AYRIGNAC Xavier, Hôpital Universitaire de Montpellier, 34000 Montpellier, x-ayrignac@chu-montpellier.fr

BOURRE Bertrand, Hopital Universitaire de Rouen, 76000 Rouen, bertrand.bourre@chu-rouen.fr

CIRON Jonathan, Hopital universitaire de Purpan, 31000 Toulouse, ciron.j@chu-toulouse.fr

COHEN Mikael, Centre Hospitalier Universitaire de Nice, 06000 Nice, cohen.m@chu-nice.fr

COLLONGUES Nicolas, Hopital universitaire de Strasbourg, 67000 Strasbourg,

nicolas.collongues@chru-strasbourg.fr

COTTON Francois, Centre Hospitalier Lyon-Sud Hospices Civils de Lyon, 69000 Lyon,

francois.cotton@chu-lyon.fr

DESCHAMPS Romain, Hôpital Fondation Adolphe de Rothschild Paris, 75019 Paris,

rdeschamps@for.paris

DURAND-DUBIEF Françoise, Hôpital Neurologique Pierre Wertheimer Hospices Civils de

Lyon, 69000 Lyon, francoise.durand-dubief@chu-lyon.fr

SAVATOVSKY Julien, Hôpital Fondation Adolphe de Rothschild Paris, 75019 Paris,

jsavatovsky@neuroradio.com

LAPLAUD David, Hopital Universitaire de Nantes, 44000 Nantes, david.laplaud@univ-

nantes.fr

MAILLART Elisabeth, Hospital de la Pitié-Salpêtrière, 75013 Paris,

elisabeth.maillart@aphp.fr

MARIGNIER Romain, Hôpital Neurologique Pierre Wertheimer Hospices Civils de Lyon,

69000 Lyon, romain.marinier@chu-lyon.fr

PAPEIX Caroline, Hôpital Fondation Adolphe de Rothschild Paris, 75019 Paris,

caroline.papeix@aphp.fr

RUET Aurelie, Hopital universitaire de Bordeaux, 33000 Bordeaux, aurelie.ruet@chu-

bordeaux.fr

KREMER Stéphane, CHU Strasbourg 67000 Strasbourg, stephane.kremer@chru-strasbourg.fr

TOURDIAS Thomas, CHU Bordeaux, 33000 Bordeaux, thomas.tourdias@chu-bordeaux.fr

VUKUSIC Sandra, Hôpital Neurologique Pierre Wertheimer Hospices Civils de Lyon, 69000 Lyon, sandra.vukusic@chu-lyon.fr

ZEPHIR Helene, Centre de ressource et competence SEP, 59000 Lille,

Helene.ZEPHIR@CHRU-LILLE.FR

## **Abbreviations**

ADEM: acute disseminated encephalomyelitis

AQP4-IgG: aquaporin-4 antibody

BSLs: bright spotty lesions

IPND: International Panel for NMO Diagnosis

ITM: idiopathic transverse myelitis

LETM: longitudinal extensive transverse myelitis

MOG-IgG: anti-myelin-oligodendrocyte glycoprotein antibodies

MS: multiple sclerosis

NMOSD: neuromyelitis optica spectrum disorder

NMOSD<sup>AQP4+</sup>: aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder

## **ABSTRACT**

### **Background and purpose:**

To determine the diagnostic value of bright spotty lesions (BSLs) for aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (NMOSD<sup>AQP4+</sup>), the predictive value of axial-BSLs for AQP4-IgG seropositivity, and the radio-clinical differences in NMOSD<sup>AQP4+</sup> patients with and without axial-BSLs.

**Materials and Methods:** Retrospective study that included patients aged  $\geq 16$  years, with a first acute spinal cord syndrome between 2005 and 2018 and abnormal spinal cord MRI with axial and sagittal T2 sequences. Patients with MRI findings consistent with compressive myelopathy were excluded. All spinal cord MRI were retrospectively evaluated for the presence of BSLs by 2 radiologists blinded to the diagnosis of acute myelopathy.

**Results:** A total of 82 patients were included; 15 aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder patients (NMOSD<sup>AQP4+</sup>), and 67 other patients, considered as the other causes of myelopathy (OM) group. The specificity of axial-BSLs for NMOSD<sup>AQP4+</sup> patients was 94.0% (95%CI [85.6 to 97.7]). The sensitivity was 40.0% (95%CI [19.8 to 64.3]). In the multivariable analysis, the only MRI characteristic associated with AQP4-IgG positivity was the presence of axial-BSLs (OR: 9.2, 95%CI [1.2 to 72.9]; p= 0.022). In NMOSD<sup>AQP4+</sup> patients, the median of cord expansion ratio was higher with axial-BSL (1.2, IQR [1.1-1.3]) than without axial-BSL (1.1, IQR [1.0-1.2]; p=0.046).

**Conclusion:** After a first acute spinal cord syndrome, the presence of axial-BSLs on spinal cord MRI seems very specific for NMOSD<sup>AQP4+</sup> and seems to be a predictor radiological marker of AQP4-IgG positivity.

**Keywords:** Neuromyelitis optica; Myelitis; MRI; Bright; Spotty

## INTRODUCTION

Neuromyelitis optica (NMO) is a rare and severe demyelinating neurological disease that mainly affects the optic nerves and the spinal cord.[1] The discovery of a pathogenic autoantibodies targeting the aquaporin-4 channel at the end-feet of the astrocytes (AQP4-IgG), a very specific biomarker of NMO, has widened the clinical phenotype of the disease and defined the neuromyelitis optica spectrum disorder (NMOSD).[2] This spectrum integrates limited forms of the disease, such as single or recurrent optic neuritis and single or recurrent myelitis tested positive for AQP4-IgG, enabling an early diagnosis and appropriated treatment.[2]

The only spinal cord imaging feature incorporated in the 2015 International Panel for NMO Diagnosis (IPND) is the presence of a longitudinal extensive transverse myelitis (LETM),

described as a T2 lesion extended to  $\geq 3$  contiguous segments, or an extended focal spinal cord atrophy.[2] However, LETM is not specific of NMOSD.[3] Other spinal cord imaging features of potential diagnostic interest have been related to NMOSD, such as bright spotty lesions (BSLs),[4] the presence of T1 dark signal,[5] and the ring enhancement pattern.[6] BSLs were proposed as a discriminative finding that helps to differentiate patients with NMOSD from those with multiple sclerosis (MS),[4] idiopathic transverse myelitis (ITM),[7] and spinal cord infarcts.[8] The presence of BSLs has also been suggested to be the most useful MRI finding for differentiating NMOSD from all the other etiologies of LETM (specificity: 89.1%; positive predictive value: 86.1%).[5]

AQP4-IgG-positive NMOSD (NMOSD<sup>AQP4+</sup>)-associated myelitis is a very severe condition for which an early and aggressive treatment is recommended to prevent disability or fatal outcome.[9,10] However such treatment is potentially harmful in patients with alternative diagnoses, including infectious myelitis and dural arteriovenous fistula.[11] As the result for AQP4-IgG and anti-myelin-oligodendrocyte glycoprotein antibodies (MOG-IgG) serostatus are frequently delayed, from 1 week to 1 month, the presence of a spinal cord radiological marker highly specific for NMOSD<sup>AQP4+</sup> at the very early stage of the spinal cord syndrome would be helpful to start the more appropriated treatment.

The aim of the present study was to determine the diagnostic value of BSLs for NMOSD<sup>AQP4+</sup> patients, to analyze the predictive value of axial-BSLs for AQP4-IgG seropositivity, and to determine the radio-clinical differences in NMOSD<sup>AQP4+</sup> patients with and without axial-BSLs.

## METHODS

Data confidentiality and safety are ensured according to the recommendations of the French *Commission Nationale Informatique et Libertés* (CNIL). NMOSD cohort is part of the OFSEP (*Observatoire de la Sclérose en Plaques*) cohort. OFSEP has received approval for storing clinical, biological, and imaging data for research purpose. Patients give informed consent for their data to be stored in the database and used for research, in France and abroad ([www.ofsep.org/en/cohort/ofsep-consent](http://www.ofsep.org/en/cohort/ofsep-consent)). The cohort has been registered to [clinicaltrials.gov](https://clinicaltrials.gov) under the number NCT02889965.

## **Patients**

Patients from the Lyon University Hospital who presented with a first acute spinal cord syndrome between 2005 and 2018 were evaluated for inclusion. Patients were identified in two databases: i) the radiology department's database (DXImage-RIS, version 5.3.19010, Dedalus FRANCE, Le Plessis-Robinson, France) using the keyword “*myélite*”; and ii) the French nationwide database for NMOSD and associated neurological disorders (NOMADMUS; part of the *Observatoire Français de la Sclérose en Plaques*, OFSEP).

Inclusion criteria were: i) clinical episode of acute spinal cord syndrome; ii) abnormal spinal cord MRI within  $\leq 3$  months of the clinical attack; and iii) age  $\geq 16$  years. Exclusion criteria were: i) patients with a previous history of spinal cord syndrome; ii) spinal cord MRI without axial T2 sequences; and iii) MRI findings consistent with compressive myelopathy.

## **Clinical characterization**

We collected the following: demographic data (age, sex), clinical data (final diagnosis, Expanded Disability Status Scale [EDSS] at nadir, EDSS at 12 months, EDSS at last follow-up, duration of follow-up, the presence of relapse, as well as acute and long-term treatment),

cerebrospinal fluid data (oligoclonal bands, pleocytosis, IgG index) and serum samples (AQP4-IgG, MOG-IgG), from medical files or the Lyon NOMADMUS database. Patients were diagnosed with MS according to 2017 McDonald criteria,[12] NMOSD according to the 2015 IPND criteria,[2] Sjogren syndrome according to the criteria defined by Vitali *et al.*,[13] acute disseminated encephalomyelitis (ADEM) according to the criteria defined by Krupp *et al.*,[14] ITM according to 2002 criteria,[15] neurosarcoidosis according to the criteria defined by Stern *et al.*,[16] Behçet's disease according to the 2014 International Criteria,[17] and systemic lupus erythematosus-associated myelitis according to the 1999 American College of Rheumatology nomenclature.[18] Parainfectious disease was defined by a previous episode of infectious symptom (*i.e.* gastroenteritis, upper respiratory tract) < 30 days before myelitis onset. Spinal cord infarct was defined by an acute myelitis with time to nadir < 24 hours.

### **Autoantibody detection**

Tests for AQP4-IgG and MOG-IgG were performed using cell-based assays with live human embryonic kidney 293 cells, as previously described.[19,20]

### **MRI parameters and review**

The MRI examinations were performed using either a 1.5T or 3T magnet from different manufacturers. Although MRI protocols were heterogeneous, all studies included axial and sagittal T2-weighted sequences of the spinal cord.

Axial-BSLs were defined as very hyper-intense spotty lesions on axial T2-WI that are visually more hyperintense or of equal signal intensity to the surrounding cerebrospinal fluid without flow void effects.[4,7] Sagittal-BSLs were defined similarly but on sagittal T2-WI (Figure 1).

In order to minimize the subjectivity of these imaging findings, all spinal cord MRI were retrospectively evaluated for the presence of axial-BSLs and/or sagittal-BSLs by 2 radiologists (1 senior resident: SR and 1 neuroradiologist with  $\geq 5$  years of expertise in neuroradiology: VNM) blinded to the final diagnosis. In cases of disagreement, the final decision was made by a third neuroradiologist with  $> 15$  years' experience (FC) also blinded to the final diagnosis.

We also evaluated the number of lesions, the size of the T2 hyperintensity signals (number of vertebral segments), the sagittal and axial lesion distribution, the T1 signal intensity of the lesion, the lesion gadolinium enhancement. Cord expansion was evaluated by the ratio of cord expansion (anteroposterior diameter of the most swollen spinal cord segment to the anteroposterior diameter of the non-involved spinal cord).

When available, we reviewed brain MRI within  $\leq 3$  months from the clinical attack. Brain MRI findings were classified as either "normal", "nonspecific lesions" or "specific lesions". When specific, lesions were subdivided into "ADEM-like", "NMO-like", "MS-like" or "Other". "ADEM-like" lesions were defined as deep gray nuclei or diffuse, poorly demarcated, large cerebral white matter lesions.[14] NMO-like lesions were defined as lesions surrounding the third and fourth ventricle, hypothalamus, dorsal medulla, area postrema, corticospinal tract, or aqueduct without imaging features suggestive of MS.[21,22] "MS-like" were defined as lesions perpendicular to a lateral ventricular surface (Dawson fingers), adjacent to lateral ventricle in the inferior temporal lobe, and/or juxtacortical lesions involving subcortical U-fibers. "Specific lesions" were classified as "other" when brain MRI findings were suggestive of another illness.

## **Statistical Analysis**

We studied and compared a group of NMOSD AQP4 + patients and a group of patients with other causes of myelopathy (OM group).

The diagnostic performances of axial-BSLs and sagittal-BSLs were evaluated by comparing the data of the NMOSDAQP4+ group with those of the OM group.

Demographic, neuroradiological and serological data were compared between the NMOSDAQP4+ group and the OM group using the Fisher's exact test or the Mann-Whitney U test for categorical or continuous variables, respectively.

For the evaluation of the presence of axial-BSLs and sagittal-BSLs on the T2 sequences, interobserver agreement was assessed using Cohen's Kappa coefficient. In the interpretation of the Kappa coefficient, the standards for strength of agreement reported by Landis and Koch were followed.[23]

Univariable logistic regression analysis was performed, and baseline variables with  $p \leq 0.10$  were included in the multivariable logistic regression analysis. Odds ratios (ORs) with 95% confidence interval (CI) were used to measure the effect of predictors. Statistical significance was set at  $p < 0.05$ . Statistical analyses were performed using the STATA-12 software (64-bit, StataCorp, College Station, TX, US) and figures using GraphPad Prism (version 5.0, GraphPad Software, La Jolla, CA, US).

## RESULTS

### **Etiology of myelitis**

A total of 82 patients with acute spinal cord syndrome were included; there were 15 (18%) NMOSD<sup>AQP4+</sup> patients and among the remaining 67 (82%) patients (OM group) 4 (5%) had a final diagnosis of NMOSD<sup>AQP4-</sup>, 4 (5%) MOG-IgG-associated myelitis, 27 (33%) MS, 15 (18%) ITM, 8 (10%) systemic disease-associated myelitis, 4 (5%) spinal cord infarcts, 3 (4%)

parainfectious myelitis, 1 (1%) ADEM, and 1 (1%) metabolic myelopathy.

Among patients with ITM, 6 (40%) had extensive and 9 (60%) had short transverse myelitis (STM); one case of ITM had relapsing disease. The patient with ADEM was 19 years of age and was seronegative for MOG-IgG. The parainfectious myelitis cases included 1 (33%) varicella-zoster virus parainfectious myelitis, 1 (33%) mycoplasma pneumoniae parainfectious myelitis, and 1 (33%) measles parainfectious myelitis. Among patients with systemic disease-associated myelitis, 4 (50%) were probable or possible neurosarcoïdosis, 2 (25%) were systemic lupus erythematosus associated myelitis, 1 (13%) was Behçet's disease associated myelitis, and 1 (13%) was Sjögren's syndrome-associated myelitis.

The clinical type of MS patients was relapsing-remitting form in all cases. Among the 4 patients with MOG-IgG-associated diseases 2 had encephalic lesions and 1 patient had with a concomitant optic neuritis.

### **Tests for AQP4-IgG and MOG-IgG**

All NMOSD patients were tested for AQP4-IgG, and 2 out of the 4 (50%) NMOSD<sup>AQP4+</sup> patients were tested for MOG-IgG. A total of 20 of 82 (24%) patients were not tested for AQP4-IgG, but did fulfil the corresponding diagnostic criteria.

### **Demographic, clinical, and laboratory features**

NMOSD<sup>AQP4+</sup> patients were more frequently woman (13/15, 86.7% vs. 36/67, 53.7%;  $p=0.039$ ) and had more frequently a relapse (14/15, 93.3% vs. 18/67, 26.9%;  $p<0.001$ ) than the OM group. There was a trend towards a greater age at onset (46.9, IQR [30.8-59.8] vs. 37, IQR [27-50] years;  $p=0.085$ ), greater EDSS at nadir (7.25, IQR [5.25-8] vs. 5, IQR [3-6.5];  $p=0.110$ ), and worse EDSS at last follow-up (4, IQR [0-5.5] vs. 2, IQR [0.5-4];  $p=0.450$ ) in

the NMOSD<sup>AQP4+</sup> patients than in the OM group. The median time from the first acute spinal cord syndrome to the spinal cord MRI study was greater in the NMOSD<sup>AQP4+</sup> group (24 days, IQR [11-88]) than in the OM group (7 days, IQR [3-16];  $p < 0.001$ , Table 1).

### **Diagnostic value of axial-BSLs**

The specificity of axial-BSLs was 94.0% (95%CI [85.6 to 97.7]) and the sensitivity was 40.0% (95%CI [19.8 to 64.3]). None of the patients with MOG-IgG-associated myelitis (0/4), MS (0/27), ITM (0/15) or spinal cord infarcts (0/4) had axial-BSLs (Table 2).

One of the 6 NMOSD<sup>AQP4+</sup> patients with STM (16.7%) had axial-BSLs. Axial-BSLs were found in 4 patients of the OM group (6%) on spinal cord MRI; 2 (50%) seronegative NMOSD patients, 1 (25%) AQP4-IgG seronegative patient with mycoplasma pneumoniae parainfectious myelitis and 1 (25%) AQP4-IgG seronegative patient with Sjögren's syndrome-associated myelitis (Figure 2). The inter-observer agreement for axial-BSLs was substantial (Kappa: 0.67, 95%CI [0.41 to 0.94];  $p < 0.001$ ).

### **Diagnostic value of sagittal-BSLs**

Sagittal-BSLs were more frequently found in the NMOSD<sup>AQP4+</sup> patients than the OM group (4/15, 26.7% vs. 1/67, 1.5%, respectively;  $p < 0.01$ ; specificity for NMOSD<sup>AQP4+</sup> was 98.5%, 95%CI [92.0 to 99.7]). Sensitivity was 26.7% (95%CI [10.9 to 52.0]). Sagittal-BSLs were observed in 1 patient of the OM group with probable neurosarcoidosis. The inter-observer agreement for sagittal-BSLs was moderate (Kappa: 0.46, 95%CI [0.10 to 0.83];  $p < 0.001$ ).

### **Factors predictive of AQP4-IgG seropositivity**

In univariable binary regression analysis, women had a greater risk for AQP4-IgG positivity

(OR: 5.6, 95%CI [1.2 to 26.7]; p=0.031) as did those with axial-BSLs (OR: 10.5, 95%CI [2.5 to 44.5]; p=0.001, Table 3). In multivariable analysis, the only independent predictor of AQP4-IgG positivity was the presence of axial-BSLs (OR: 9.2, 95%CI [1.2 to 72.9]; p=0.035).

### **Differences between NMOSD<sup>AQP4+</sup> patients with or without axial-BSLs**

The median of cord expansion ratio was higher in the axial-BSL-positive NMOSD<sup>AQP4+</sup> patients (1.2, IQR [1.1-1.3]) than in the axial-BSL-negative NMOSD<sup>AQP4+</sup> patients (1.1, IQR [1.0-1.2]; p=0.046). There was a trend towards a greater median of EDSS at nadir (8, IQR [7.5-8] vs. 5.25, IQR [2.75-7.25], respectively; p=0.053), median of last EDSS (4.75, IQR [4-5.5] vs. 1, IQR [0-6], respectively; p=0.250), and frequency of last EDSS  $\geq 3$  (4/4, 100% vs. 3/7, 42.9%, respectively; p=0.194) in the axial-BSLs-positive NMOSD<sup>AQP4+</sup> patients than in axial-BSLs-negative NMOSD<sup>AQP4+</sup> patients. Age at onset, sex, the LETM pattern, hypointensity on T1-WI and time from the first acute spinal cord syndrome to the spinal cord MRI study did not differ significantly (Table 4).

## **DISCUSSION**

In the present study, we confirm that axial-bright spotty lesions (axial-BSLs) is a useful marker to discriminate aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (NMOSD<sup>AQP4+</sup>) patients from alternative diagnoses including MS, spinal cord infarcts, and other neuro-inflammatory disorders presenting as myelitis. Moreover, the presence of axial-BSLs on spinal cord MRI was a predictive factor of AQP4-IgG seropositivity.

The pathophysiology of BSLs remains unknown but could reflect necrotic areas with cystic inflammatory lesions due to astrocytic impairment associated with the loss of AQP4 that have

been described by Sato *et al.* on biopsied AQP4-IgG-positive myelitis.[24] We can also assume that these lesions are transient; Hyun *et al.* found axial-BSLs tended to disappear during MRI follow-up.[7]

Axial-BSLs were absent in MS and also MOG-IgG-associated myelitis, both characterized by predominant demyelination. Differences in anatomopathological features between MS lesions and NMOSD lesions may explain these findings.[25,26] Although, pathological findings of MOG-IgG-associated myelitis at the acute stage is largely unknown, the absence of axial-BSLs supports the hypothesis that its pathogenesis is distinct from that of NMOSD.[27,28]

Axial-BSLs were found in 4 AQP4-IgG-seronegative patients, only 2 of which did not fulfill the diagnostic criteria for NMOSD but had a parainfectious myelitis and a systemic autoimmune diseases-associated myelitis. Therefore, the presence of axial-BSLs should be an argument in favor of the diagnosis of NMOSD. This could be particularly useful during an acute spinal cord syndrome when there is no other core clinical characteristic of the 2015 IPND criteria (optic neuritis, area postrema syndrome, acute brainstem syndrome, diencephalic clinical syndrome or cerebral syndrome).[2]

Presence of axial-BSLs were not significantly associated with a higher EDSS at nadir in NMOSD<sup>AQP4+</sup> patients, as previously reported.[7] However, there was a trend towards a worse median EDSS at nadir, a worse median EDSS at 12 months and worse median EDSS at last follow-up in the NMOSD<sup>AQP4+</sup> patients than in the OM group. This possible association, suggesting that axial-BSLs could be a marker of poor prognosis would need further evaluation.

Although Pekcevik *et al.* have described the presence of BSLs on T2-weighted sagittal image in the legend of their figure,[5] all previous studies have studied BSLs only on axial T2 sequences.[4,5,7,8,29] We supposed that BSLs could also be recognized on sagittal T2 sequences. Sagittal-BSLs had a very high specificity for NMOSD<sup>AQP4+</sup> but there was a trend

towards lower sensitivity and inter-observer agreement than for axial-BSLs, probably because of the lower spatial resolution of sagittal T2-WI due to slice thickness. In addition, the absence of a sagittal-BSL did not mean the absence of axial-BSLs. Performing an axial T2-WI therefore remains essential to characterize the spinal cord lesion.

The 2015 IPND criteria gives a key place to the LETM pattern for NMOSD diagnosis, describing it as the most specific neuroimaging characteristic of NMOSD.[2] However, LETM pattern is not pathognomonic and can be observed in infectious, vascular, metabolic or systemic diseases related myelopathy.[30] In the present study, there was a trend towards better sensitivity for LETM, but had a lower specificity than axial-BSLs to discriminate NMOSD<sup>AQP4+</sup> patients. Moreover, we found that axial-BSLs may be present with the absence of LETM. LETM and BSLs are therefore complementary in the diagnosis of NMOSD. Accordingly, the next revision of the diagnostic criteria for NMOSD could include BSLs as a discriminating finding in acute myelitis, especially when serological tests for AQP4-IgG are not available or negative.

Finally, we did not find T1 dark signal in NMOSD<sup>AQP4+</sup> patients. The presence of this finding seems less clear than that of the axial-BSLs and their distinction with a simple T1 hypointensity is sometimes equivocal, probably in relation to a contrast resolution of the T1-WI lower than that of the T2-WI.

The present study has the inherent limitations of a retrospective study. For instance, serological tests for AQP4-IgG or MOG-IgG were not available for all patients (20 out of 82 patients not tested for AQP4-IgG) but they were available for all NMOSD patients, MOG-IgG seropositive patients and axial-BSLs-positive patients. Our study sample includes a limited number of patients because the disease studied is a rare disease. Another point is that, although the most common causes of acute myelopathy were included in the OM group, some causes such as arteriovenous fistula, radiation myelopathy or paraneoplastic myelopathy were

not represented, probably because of the method used to identify the patients. On the other hand, despite a potential negative influence on the diagnostic performance of BSLs, NMOSD<sup>AQP4-</sup> and MOG-IgG seropositive patients were not excluded from the OM group, and, unlike previous studies,[5,29] the population was not limited to LETM. It is also of note that the inter-rater agreement for the axial-BSLs was not high but substantial according to the Landis and Koch kappa's benchmark scale and not lower than that previously observed (ranging from 0.61 to 1).[4,29] A strength of the study only the first spinal cord syndrome in order to avoid the effects of anterior spinal cord lesions and their treatments on the imaging aspect, however, MRI machines and protocols were heterogeneous as in clinical routine.

In conclusion, the diagnostic value of axial-bright spotty lesions (axial-BSLs) for aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (NMOSD<sup>AQP4+</sup>) at first acute spinal cord syndrome is very interesting with a high specificity. Furthermore, axial-BSLs seems to be a predictor radiological marker of aquaporin-4 antibody (AQP4-IgG) positivity. Finally, the only significant radio-clinical difference in NMOSD<sup>AQP4+</sup> patients with and without axial-BSLs, was the median of cord expansion ratio, higher in patients with axial-BSL.

**Funding:** This work has been supported by a grant provided by the French State and handled by the "Agence Nationale de la Recherche," within the framework of the "Investments for the Future" program, under the reference ANR-10-COHO-002.

**Acknowledgements:** This work has been done by using data from the *Observatoire Français de la Sclérose en Plaques* (OFSEP) which is supported by a grant provided by the French State and handled by the "Agence Nationale de la Recherche", within the framework of the "Investments for the Future" programme, under the reference ANR-10-COHO-002

*Observatoire Français de la Sclérose en Plaques (OFSEP)*, and by the Eugene Devic  
Foundation against Multiple Sclerosis (EDMUS Foundation).

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## TABLES

**Table 1.** Demographic, clinical and laboratory features of the study sample

	NMOSD <sup>AQP4+</sup> n=15	OM group n=67	Total n=82
Demographic features			
Woman, n (%)	13 (87)	36 (54)	49 (60)
Age at onset, years, median [IQR]	47 [31-60]	37 [27-50]	40 [29-53]
Clinical features			
Duration of follow-up, months, median [IQR]	71.8 [57.4-98.8]	26.8 [12.2-49.3]	30.67 [14.9-65.1]
EDSS at nadir, median [IQR]	7.25 [5.25-8]	5 [3-6.5]	5 [3-7.5]
EDSS at 12 months, median [IQR]	6 [3-6.5]	2 [1-4]	2.25 [1-5.5]
Relapse, n (%)	14 (93.3)	18 (26.9)	32 (39.0)
ARR, median [IQR]	0.3 [0.2-0.4]	0 [0-0.2]	0 [0-0.4]
Last EDSS, median [IQR]	4 [0-5.5]	2 [0.5-4]	2 [0-5]
EDSS < 3.0, n (%)	4 (36.4)	38 (55.2)	42 (53.9)
EDSS ≥ 3.0, n (%)	7 (63.6)	29 (44.8)	36 (46.1)
Laboratory data			
CSF oligoclonal bands, n (%)	2 (25)	28 (44.4)	30 (42.3)
Pleocytosis (> 5 cells/mm <sup>3</sup> ), n (%)	5 (38.5)	35 (55.6)	40 (52.6)
IgG index (> 0.7), n (%)	2 (25)	22 (37.3)	24 (35.8)
Test for AQP4-IgG, n (%)	15 (100)	47 (70.2)	62 (75.6)
Test for MOG-IgG, n (%)	5 (33.3)	25 (37.3)	30 (36.6)
Radiological features			
LETM, n (%)	9 (60)	26 (38.8)	35 (42.7)
Cord expansion ratio, median [IQR]	1.1 [1.1-1.2]	1.1 [1.0-1.2]	1.1 [1.0-1.2]
Area postrema involvement, n (%)	5 (35.7)	3 (4.6)	8 (10.1)

Axial-BSLs, n (%)	6 (40)	4 (6)	10 (12.2)
Sagittal-BSLs, n (%)	4 (26.7)	1 (1.5)	5 (6.1)
T1 dark signal, n (%)	0 (0)	1 (2)	1 (1.7)
T1 hypointensity, n (%)	5 (50)	7 (14.3)	12 (20.3)
Ring-enhancement, n (%)	7 (50)	4 (6.8)	7 (9.6)
Treatment data			
Acute treatment, n (%)	15 (100)	63 (94.0)	78 (95.1)
Long-term treatment, n (%)	12 (80)	38 (56.7)	50 (61.0)

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ARR, annualized relapse rate; AQP4-IgG, anti-aquaporin-4 antibodies; Axial-BSLs, Bright spotty lesions on axial T2-weighted images; CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; IgG, Immunoglobulin G; LETM, longitudinal extensive transverse myelitis; MOG-IgG, anti-myelin-oligodendrocyte glycoprotein antibodies; NMOSD<sup>AQP4+</sup>, AQP4-IgG-positive neuromyelitis optica spectrum disorder patients; OM, Other causes of myelopathy; Sagittal-BSLs, Bright spotty lesions on sagittal T2-weighted images.

**Table 2.** Diagnostic performance of axial-BSLs, of sagittal-BSLs, and LETM to discriminate NMOSD<sup>AQP4+</sup> patients at first acute spinal cord syndrome

	NMOSD <sup>AQP4+</sup> vs. OM group		
	Axial-BSLs	Sagittal-BSLs	LETM
Sensitivity, % [95%CI]	6/15, 40.0 [19.8; 64.3]	4/15, 26.7 [10.9; 52.0]	9/15, 60.0 [35.8; 80.2]
Specificity, % [95%CI]	63/67, 94.0 [85.6; 97.7]	66/67, 98.5 [92.0; 99.7]	41/67, 61.2 [49.2; 72.0]
PPV, % [95%CI]	6/10, 60.0 [31.3; 83.2]	4/5, 80.0 [37.6; 96.4]	9/35, 25.7 [14.2; 42.1]
NPV, % [95%CI]	63/72, 87.5 [77.9; 93.3]	66/77, 85.7 [76.2; 91.8]	41/47, 87.2 [74.8; 94.0]

Axial-BSLs, Bright Spotty Lesions on axial T2-weighted images; LETM, longitudinal extensive transverse myelitis; NMOSD<sup>AQP4+</sup>, anti-aquaporin-4 antibodies-positive neuromyelitis optica spectrum disorder patients; NPV, negative predictive value; OM: Other causes of myelopathy; PPV, positive predictive value; Sagittal-BSLs, Bright Spotty Lesions on sagittal T2-weighted images.

**Table 3.** Factors predictive of AQP4-IgG seropositivity

	OR [95%CI]	P value
Age at onset	1.0 [1.0; 1.1]	0.111
Woman	5.6 [1.2; 26.7]	0.031
EDSS at nadir	1.4 [0.9; 2.0]	0.104
CSF oligoclonal bands	0.4 [0.1; 2.2]	0.306
Pleocytosis	1.0 [1.0; 1.0]	0.404
Axial-BSLs	10.5 [2.5; 44.5]	0.001
Sagittal-BSLs	24 [2.4; 235.2]	0.006
LETM	2.4 [0.8; 7.4]	0.140
Size of the spinal cord lesion	1.1 [1.0; 1.2]	0.252
Ring-enhancing lesion	3.8 [0.7; 19.2]	0.112
Central lesion	2.1 [0.5; 8.2]	0.288
>1/2 of the cord area	3.0 [0.9; 9.6]	0.071
Medulla oblongata involvement	5.3 [0.7; 41.0]	0.114
Cord expansion ratio	3.2 [0.0; 247.1]	0.604
NMO-like on initial brain MRI	0.4 [0.1; 1.4]	0.170

AQP4-IgG, anti-aquaporin-4 antibodies; Axial-BSLs, Bright Spotty Lesions on axial T2-weighted images; CI, confidence interval; CSF, Cerebrospinal fluid; EDSS, Expanded Disability Status Scale; LETM, longitudinal extensive transverse myelitis; MRI, magnetic resonance imaging; NMO, neuromyelitis optica; OR, odds ratio; Sagittal-BSLs, Bright Spotty Lesions on sagittal T2-weighted images.

**Table 4.** Differences between NMOSD<sup>AQP4+</sup> patients with or without axial-BSLs

	Axial-BSL+	Axial-BSL-	P value
	n=6	n=9	
Cord expansion ratio, median [IQR]	1.2 [1.1-1.3]	1.1 [1.0-1.2]	0.046
EDSS at nadir, median [IQR]	8 [7.5-8]	5.25 [2.75-7.25]	0.053
EDSS at 12 months, median [IQR]	6.25 [5.75-6.75]	3 [2-6.5]	0.389
Last EDSS, median [IQR]	4.75 [4-5.5]	1 [0-6]	0.250
Last EDSS $\geq$ 3.0, %	100	42.7	0.194
Age at onset, median [IQR]	42 [30-60]	47 [41-57]	0.724
Woman, %	83	89	1.000
LETM, %	83.3	44.4	0.287
T1 hypointensity, %	60	40	1.000
Ring-enhancing lesion, %	40	11.1	0.505
Size of the spinal cord lesion, vertebral segment, median [IQR]	3.5 [3-5]	1 [1-4]	0.206
Time from onset to initial spinal cord MRI, days, median [IQR]	11.5 [6-4]	53 [15-88]	0.087

Axial-BSLs+, Bright Spotty Lesions on axial T2-weighted images positive; Axial-BSLs-, Bright Spotty Lesions on axial T2-weighted images negative; EDSS, Expanded Disability Status Scale; LETM, longitudinal extensive transverse myelitis; MRI, magnetic resonance imaging; NMOSD<sup>AQP4+</sup>, anti-aquaporin-4 antibodies-positive neuromyelitis optica spectrum disorder.

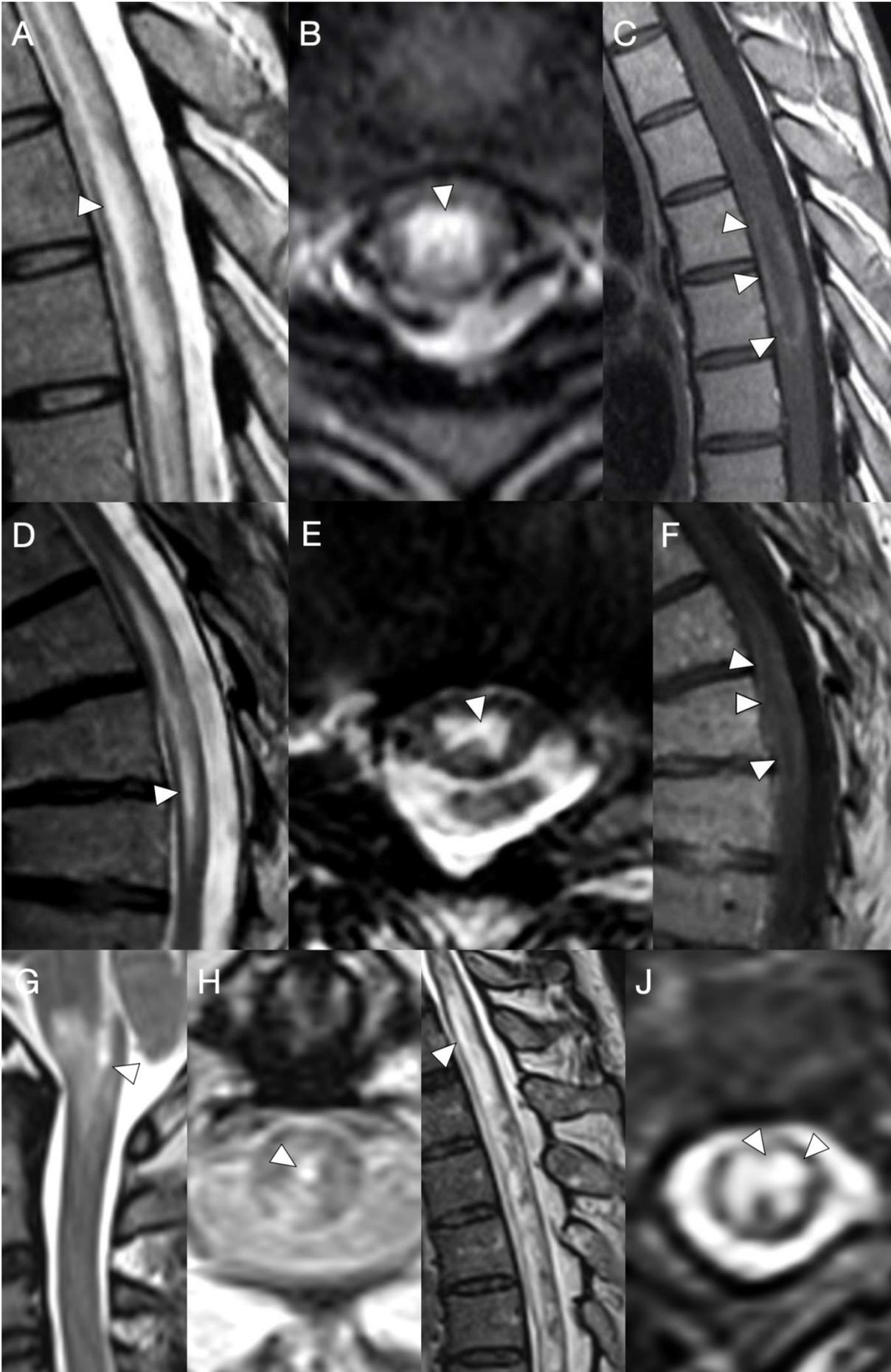
## FIGURE LEGENDS

### **Figure 1.** Sagittal-BSLs in 4 NMOSD<sup>AQP4+</sup> patients.

T2-weighted sagittal images show LETM with sagittal-BSLs (arrowheads; A, D, G, I). BSLs are also present on T2-weighted axial images (arrowheads; B, E, H, J). Sagittal contrast-enhanced T1-weighted images show a ring-enhancement (arrowheads) of the LETM in 2 patients (C, F). BSLs, bright spotty lesions; LETM, longitudinally extensive transverse myelitis; NMOSD<sup>AQP4+</sup>, anti-aquaporin-4 antibodies-positive neuromyelitis optica spectrum disorder.

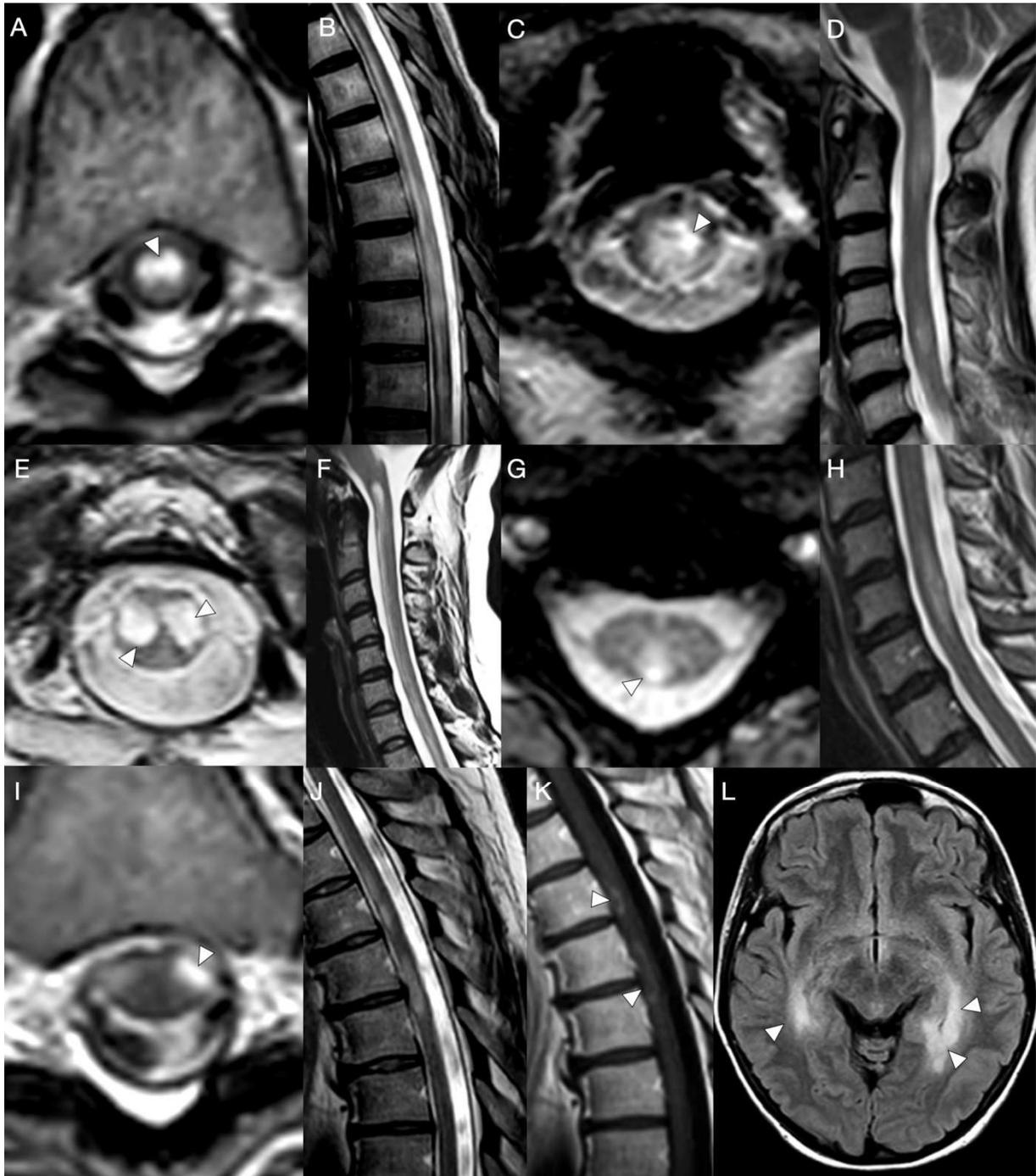
### **Figure 2.** Anti-aquaporin-4 antibodies-negative patients with axial-BSLs.

Spinal cord MRI of NMOSD<sup>AQP4-</sup> patient (A-D). LETM involving thoracic and cervical spinal cord extending into the area postrema with BSLs (arrowheads) on the thoracic and cervical T2-weighted axial images. Spinal cord MRI of NMOSD<sup>AQP4-</sup> patient (E, F). T2-weighted sagittal image shows LETM extending into the brainstem and T2-weighted axial image shows BSLs (arrowheads). Spinal cord MRI of patient with mycoplasma pneumoniae parainfectious myelitis (G, H). Cervical myelitis with BSLs (arrowhead) on a T2-weighted axial image. Spinal cord and brain MRI of patient with Sjögren's syndrome-associated myelitis (I-L). A short transverse myelitis involving thoracic spinal cord with BSLs (arrowhead) on a T2-weighted axial image (I, J). Sagittal contrast-enhanced T1-weighted image show a ring-enhancement (arrowheads) of the short myelitis (K). Axial FLAIR image shows hyperintense lesions (arrowheads) involving the periependymal surfaces of the lateral ventricles (L). BSLs, bright spotty lesions; FLAIR, Fluid-attenuated inversion recovery; LETM, longitudinally extensive transverse myelitis; NMOSD<sup>AQP4-</sup>, anti-aquaporin-4 antibodies-negative neuromyelitis optica spectrum disorder.



**Figure 1.** Sagittal-BSLs in 4 NMOSD<sup>AQP4+</sup> patients.

T2-weighted sagittal images show LETM with sagittal-BSLs (arrowheads; A, D, G, I). BSLs are also present on T2-weighted axial images (arrowheads; B, E, H, J). Sagittal contrast-enhanced T1-weighted images show a ring-enhancement (arrowheads) of the LETM in 2 patients (C, F). BSLs, bright spotty lesions; LETM, longitudinally extensive transverse myelitis; NMOSD<sup>AQP4+</sup>, anti-aquaporin-4 antibodies-positive neuromyelitis optica spectrum disorder.



**Figure 2.** Anti-aquaporin-4 antibodies-negative patients with axial-BSLs.

Spinal cord MRI of NMOSD<sup>AQP4-</sup> patient (A-D). LETM involving thoracic and cervical spinal cord extending into the area postrema with BSLs (arrowheads) on the thoracic and cervical T2-weighted axial images. Spinal cord MRI of NMOSD<sup>AQP4-</sup> patient (E, F). T2-weighted sagittal image shows LETM extending into the brainstem and T2-weighted axial image shows BSLs

(arrowheads). Spinal cord MRI of patient with mycoplasma pneumoniae parainfectious myelitis (G, H). Cervical myelitis with BSLs (arrowhead) on a T2-weighted axial image. Spinal cord and brain MRI of patient with Sjögren's syndrome-associated myelitis (I-L). A short transverse myelitis involving thoracic spinal cord with BSLs (arrowhead) on a T2-weighted axial image (I, J). Sagittal contrast-enhanced T1-weighted image show a ring-enhancement (arrowheads) of the short myelitis (K). Axial FLAIR image shows hyperintense lesions (arrowheads) involving the periependymal surfaces of the lateral ventricles (L). BSLs, bright spotty lesions; FLAIR, Fluid-attenuated inversion recovery; LETM, longitudinally extensive transverse myelitis; NMOSD<sup>AQP4-</sup>, anti-aquaporin-4 antibodies-negative neuromyelitis optica spectrum disorder.

