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Evaluation of the NMOSD 2015 imaging guideline to differentiate between diagnosis of multiple sclerosis and neuromyelitis optica spectrum disorder in Thai patients

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Abstract

Background & Objective: The neuromyelitis optic spectrum disorders (NMOSD) diagnostic criteria introduced in 2015 proposed many imaging criteria to differentiate between NMOSD and multiple sclerosis (MS). Criteria applied in Asian population with higher prevalence of NMOSD might not be as specific. The objective was to evaluate the NMOSD 2015 imaging guideline in Thai patients. *Methods:* The patients were recruited from MS and Related Disorders Clinic at a university hospital. NMOSD 2015 and McDonald 2010 diagnostic criteria were applied for diagnosis. NMOSD was classified into positive- and negative-AQP4 groups.The MRI available in the institute PAC system was reviewed by 3 neuroradiologists for features according to NMOSD 2015 imaging criteria. Percentage of each finding was calculated in all groups. *Results:* There were 37 MS and 101 NMOSD patients, with positive- and negative-AQP4 NMOSD in 88 and 13 cases, respectively. Most of the patients were female. Findings in brain MRI suggestive of MS were Dawson finger sign, periventricular inferior temporal lobe and corticospinal tract lesions. Involvement of corpus callosum and optic pathway was more common in MS. More patients with NMOSD showed involvement at posterior half of the optic nerve, whereas more patients with MS had involvement of optic radiation and optic tract. Spinal cord lesions more common in NMOSD included thoracic cord involvement, lesions extending more than 3 vertebral body segments and centrally located lesions in axial plane.
Conclusion: Only some brain MRI features were more conclusive for NMOSD in Thai patients. Spinal cord MRI lesions were still more helpful in differentiating between MS and NMOSD.

Keywords: MRI,multiple sclerosis, neuromyelitis optica, transverse myelitis, optic neuritis

INTRODUCTION

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are inflammatory diseases of the central nervous system with different pathogenesis and treatment regimens.[1] MS is much more common, with approximately half of those affected in Europe.[2] NMOSD also occurs worldwide but the global incidence and prevalence are still incompletely characterized.[3] The revised McDonald criteria 2010 require clinical as well as magnetic resonance imaging criteria for diagnosis.[4] Recently, the International Panel for NMO Diagnosis (IPNRD) has proposed diagnostic criteria using core clinical features, aquaporin-4 (AQP-4) serology status and imaging features.[5] In the clinical practice, however, even with the guideline, some clinical presentations and neuroimaging features are often overlapping and not always distinguishable between these diseases.[6]Thus, it's a challenge to give a correct diagnosis without available serological testing.

The importance of early diagnosis and early treatment to prevent disability in NMOSD and MS have been stressed upon. However, the key is to arrive at the correct diagnosis, as disease modifying therapies (DMTs) for MS can be deleterious in NMOSD patients. Several studies offered clues to differentiate between the two, the MAGNIMS consensus guideline for MS is

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one.[4]This is especially important in Thailand as the incidence of MS was lower than Western countries, estimated to be 1-2 /100,000 population, and similar to other Asian countries.[7]The high incidence of NMOSD in Thai patients may mislead clinicians who rely on only clinical and imaging findings and without serological result. We aim to evaluate NMOSD 2015 imaging criteria to distinguish NMOSD and MS in a population which incidence of the latter is low.

METHODS

This is a retrospective study on patients from MS and Related Disorders clinic at Siriraj Hospital, Bangkok, Thailand. The Siriraj Institutional Review Board approved the study, protocol number 015/2559(EC4). Patients gave their written informed consents.

Diagnosis was according to the NMOSD 2015 and the Revised McDonald 2010 criteria for MS. Final diagnosis was based on consensus by at least 3 neurologists. Patients were classified into 3 groups, NMOSD with or without AQP4 antibody and MS.[4,5] Those with other causes of inflammatory demyelinating diseases were excluded.

The magnetic resonance imaging (MRI) were performed on 3-Tesla (Philips MR Systems, Ingenia, Best, the Netherlands) and 1.5-Tesla (Philips MR Systems, Archieva, Best, the Netherlands) scanners. Studies composed of brain, optic pathway and spinal cord with gadolinium (Gd) enhancement. Brain MRI included axial (T1WI, T2WI, fluid-attenuated inversion recovery:- FLAIR, DWI, T1WI/Gd), coronal (T2W, T1WI/Gd) and sagittal (T1WI, T2WI/FLAIR and T1WI/Gd) planes. Thickness of axial plane varied from 3-5 mm. Optic pathway MRI was performed on axial and coronal views with fat suppression (FS) as T2WI/FS and T1WI/Gd/FS. Spinal MRI was performed with screening sagittal T2WI of the whole spine cord. If a lesion was detected on sagittal T2WI, axial T2WI scans with or without T1WI/Gd/FS at the level with visualized lesion, would be performed.

The first brain, optic pathway and spinal MRI available on the hospital PAC system were reviewed with description according to NMOSD 2015 imaging guideline. Three neuroradiologists with more than 5 years experiences, blinded to the clinical data, separately reviewed the scans. Findings of each imaging features were collected. Data was described in frequency and calculated in percentage. Binary logistic regression of each finding and in collective was employed to differentiate between NMOSD and MS. Results was displayed as odds ratio (OR) and 95% CI. Inter-observer agreement of all findings was calculated for Kappa values.

RESULTS

We recruited 138 patients. There were 37, 88 and 13 patients with MS, positive-AQP4 NMOSD and AQP4-negative NMOSD, respectively. There was no difference in the age of first attack between each group. Female sex was more common in all groups. (Table 1)

Brain MRI findings

Brain MRI were available in all 37 MS and 13 negative-AQP4 NMOSD patients and only in 83 of 88 positive-AQP4 NMOSD cases. Findings significantly more common in MS than NMOSD were Dawson finger sign, lesions at periventricular inferior temporal area, hypothalamus/thalamus and cortical gray, in that order. Juxtacortical lesion was also more common but did not reach statistical significance (Table 2, Figure 1).

As regards to corpus callosum, significant difference of lesion patterns was perpendicular orientation and inner half involvement, of which were found more in MS group. (Table 3, Figure 2)

Table 1: Demographic dataof the study patients

	Multiple Sclerosis (37)	Neuromyelitis Optica Spectrum Disorder	
		Positive-AQP4 (88)	Negative-AQP4 (13)
Age at first attack (years) mean ± SD (range))	34 ± 13.39 (16-67)	39.9 ± 16.03 (15-84)	40 ± 12.6 (19-64)
Time of MRI from first attack (months)	0.5-372	0.7-336	0.2-48
Sex (female: male)	30:7	85:3	8:5

Table 2: Brain MRI findings of the study patients

Location/feature	Multiple Sclerosis		Neuromyelitis Optica Spectrum Disorders				
			Positive-AQP4		Negative-AQP4		
Number available/total; %	**37/37**	**%**	**83/88**	**%**	**13/13**	**%**	**P value***
No brain lesion	0	0	10	12.0	2	15.4	
Juxtacortical	32	86.5	59	71.0	9	69.2	0.081
Periventricular inferior temporal	26	70.0	35	42.2	6	46.0	0.005
Dawson fingers	22	59.5	4	4.8	2	15.4	<0.001
Corticospinal tract	16	43.2	15	18.6	1	7.7	0.010
Extensive white matter	15	40.5	6	7.2	3	23.0	<0.001
Hypothalamus/thalamus	11	29.7	11	13.3	1	7.7	0.029
Cortical gray	9	24.3	8	9.6	1	7.7	0.039
Subependymal (4th ventricle)	18	48.6	32	38.6	8	61.5	0.192
Area postrema	10	27.0	17	20.5	4	30.8	0.429
Mass effect	0	0	1	1.2	0	0	

* Between multiple sclerosis and positive-AQP4 Neuromyelitis Optica Spectrum Disorders

Optic nerve MRI

Optic nerve MRI were available only in 30 of 37 MS patients, 58 of 83 positive-AQP4 NMOSD patients and 12 of 13 AQP4-negative NMOSD patients. Involvement of the posterior half of optic nerve was more common in NMOSD, on the contrary, optic tract and optic radiation involvement were more in MS.(Table 4, Figure 3)

Spinal MRI findings

Spinal MRI was available in 31, 80 and 13 of MS, positive-AQP4 and negative-AQP4 NMOSD groups, respectively. Cervical and thoracic cord lesions were more common in NMOSD. Cervical lesion with medullary extension was found more often in NMOSD, although not statistically significant. Longitudinally extensive spinal cord

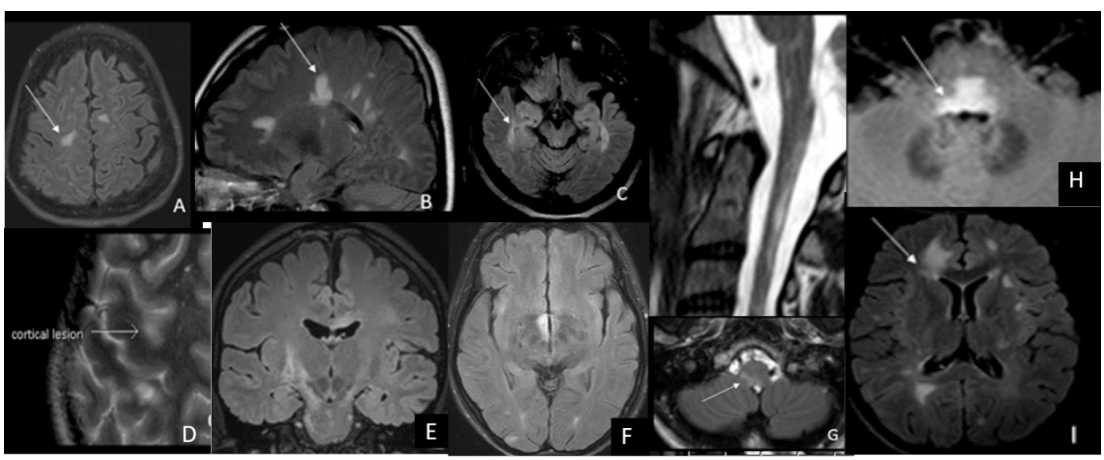

Figure 1. Brain lesions: (A) Juxtacortical lesions involving subcortical U-fibers; (B) Lesions with orientation perpeandicular to a lateral ventricular surface (Dawson's fingers); (C) Lesions adjacent to lateral ventricle in the inferior temporal lobe; (D) Cortical lesions; (E) Long corticospinal tract lesions, unilateral or bilateral, contiguously involving internal capsule and cerebral peduncle.; (F) Lesions involving the hypothalamus, thalamus, or periependymal surfaces of the third ventricle; (G) Lesions involving the dorsal medulla (especially the area postrema), either small and localized, often bilateral, or contiguous with an upper cervical spinal cord lesion; (H) Periependymal surfaces of the fourth ventricle in the brainstem/cerebellum; (I) Large, confluent, unilateral, or bilateral subcortical or deep white matter lesions

Table 3: Corpus callosal MRI findings of the study patients

Location/feature	Multiple Sclerosis		Neuromyelitis Optica Spectrum Disorders				
			Positive-AQP4		Negative-AQP4		
Number available/total; %	**37/37**	**%**	**83/88**	**%**	**13/13**	**%**	**P value***
No lesion	13	35.0	54	65.0	10	77.0	
Perpendicular	13	35.0	7	8.4	1	7.7	<0.001
Longitudinal	16	43.2	21	25.3	2	15.4	0.052
Inner half of corpus callosum	24	64.9	28	33.7	2	15.4	<0.002
Outer half of corpus callosum	1	2.7	11	13.3	1	7.7	0.109
Whole/bridging	5	13.5	12	14.5	2	15.4	<0.550

* Between multiple sclerosis and positive-AQP4 Neuromyelitis Optica Spectrum Disorders

lesion (LESCL), defined as lesions longer than 3 vertebral bodies, and lesions centrally located on axial plane (more than 70%) as well as swelling or atrophic change of spinal cord were found more often in NMOSD. (Table 5, Figure 4)

MRI findings significantly different between MS and positive-AQP4 NMOSD groups, with best adjusted odds ratio, were Dawson finger sign, thoracic cord involvement and LESCL. (Table 6)

Most findings in brain, optic nerve and spinal MRI showed excellent Kappa value (0.7-1).

DISCUSSION

Prevalence of demyelinating disease is different among different geography and ethnic groups. In the past, most studies on MS and neuromyelitis optica (NMO) were from western countries. Thus, problems arise when applying guidelines in Asian population. MS diagnosis in Thai patientsusing only McDonald criteria is not specific enough if AQP-4 testing was not done[8] due to overlapping imaging features in MS and NMOSD. Using only clinical and imaging criteria often leads to incorrect diagnosis and inappropriate management of the patient.[7] Newly proposed guidelines should be evaluated for specificity before applying in Thai patients because of the high prevalence of NMOSD. Prevalence of demyelinating disease is different among different geography and ethnic groups. In the past, most studies on MS and NMO were from western countries. Thus, problems arise when applying guidelines in Asian population. MS diagnosis in Thai patientsusing only McDonald criteria is not accurate enough if AQP-4 testing was not done[8] due to overlapping imaging features in MS and NMOSD. Using only clinical and imaging criteria often leads to incorrect diagnosis and inappropriate management of the patient.[7] Lack of specificity in brain MRI was also found among Malaysian patients.[9] Newly proposed guidelines should be evaluated for specificity before applying in Thai patients because of the high prevalence of NMOSD.

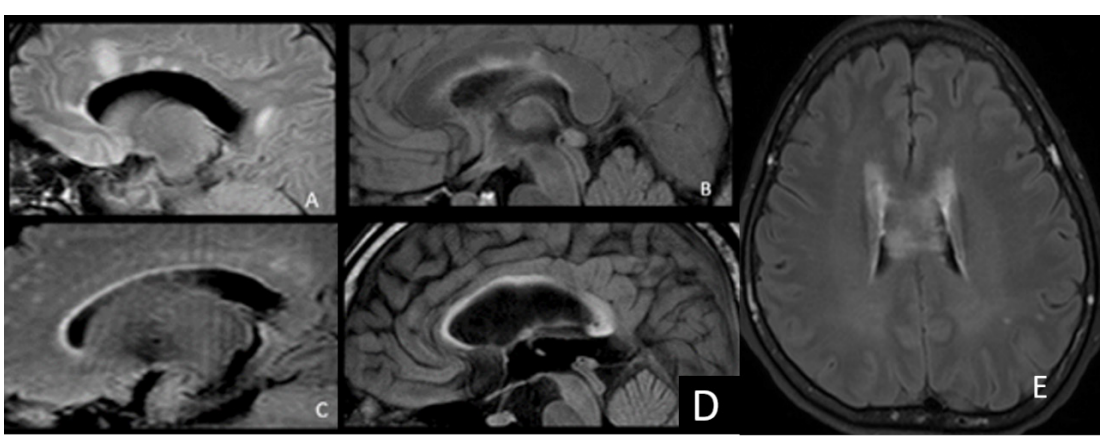

Figure 2. Callosal lesion (A) Perpendicular lesion; (B) Longitudinal lesion; (C) Inner half, (D) Inner and outer halves = whole; (E) Arch or bridge liked

Table 4: Optic pathway MRI findings of the study patients

Location	Multiple Sclerosis		Neuromyelitis Optica Spectrum Disorders				
			Positive-AQP4		Negative-AQP4		
Optic nerve (number)	**30**	**%**	**58**	**%**	**12**	**%**	**P value***
Negative optic pathway	2/30	6.7	12/58	20.7	4/12	33.3	
Anterior half optic nerve	3/30	10.0	10/58	17.2	0	0	0.370
Posterior half optic nerve	1/30	3.3	27/58	46.6	4/12	33.3	0.020
Optic chiasm	4/30	13.3	16/58	27.6	1/12	8.3	0.226
Optic tract	16/30	53.3	6/83**	7.2	0	0	<0.001
Optic radiation (number)	**34**	**%**	**83**	**%**	**13**	**%**	
No lesion	7/34	20.6	45/83	54.2	7/13	53.8	
Lesion present	27/34	79.4	38/83	45.8	6/13	46.2	**0.001**

* Between multiple sclerosis and positive-AQP4 Neuromyelitis Optica Spectrum Disorders;
** Optic tract was evaluated from brain MRI

We found that in Thai patients, the MRI features with highest predictive values to separate MS from NMOSD were Dawson finger sign for MS and LESCL for NMOSD. In the real world of practice, when serological test is not done or not available, these MRI findings may be useful. Our study also showed that other typical MRI features proposed in the NMOSD-2015 guideline overlapped with MS groups.

Information from both brain and spinal MRI are adjunctive. We proposed an approach for differential diagnosis. When there is Dawson finger sign and no LESCL, the probability of having MS is high. With the opposite findings, NMOSD is more likely. Otherwise, it is difficult to separate MS and NMO with certainty by using combinations any other these two findings. AQP-4 antibody testing is necessary in Thai patients. (Figure 5)

The retrospective study design and incomplete MRI data were the major limitations of our study. The small number of patients in subgroup analysis of some MRI features may limit its power to detect statistical significances, given that some of these features reached significance in univariate analyses. Anti-MOG antibody, which was reported

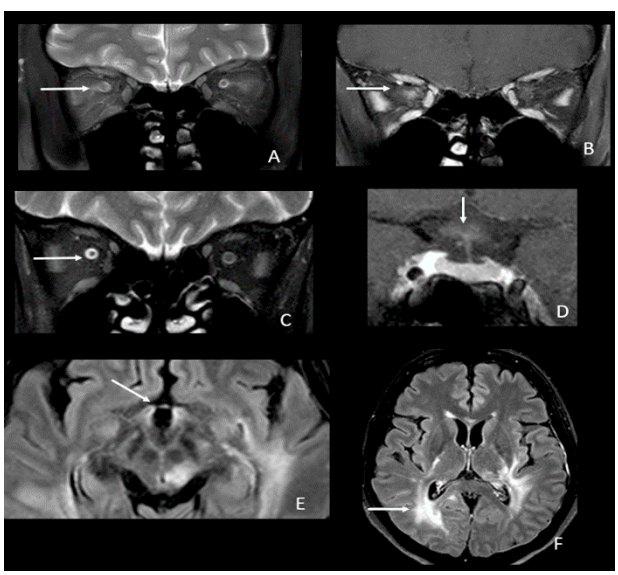

Figure 3. Optic MRI. Unilateral right optic neuritis along intraorbital part on coronal (A) T2WI/FS and (B) on coronal T1WI/Gd/FS; (C) Right optic nerve atrophy on coronal T2WI/FS; (D) Optic neuritis at optic chiasm on coronal T1WI/Gd/FS; (E) Involvement at both optic tract; (F) Involvement of optic radiation

Table 5: Spinal cord MRI findings of the study patients

Location	Multiple Sclerosis		Neuromyelitis Optica Spectrum Disorders				
			Positive-AQP4		Negative-AQP4		
Number available/total; %	**31**	**%**	**80**	**%**	**13**	**%**	**P value***
Negative	13	41.9	5	6.0	3	23.0	
Cervical to medulla	6	19.4	20	24.0	5	38.5	0.530
Cervical	15	48.4	58	72.5	9	69.2	0.006
Thoracic	9	29.03	68	85.0	4	30.8	< 0.001
< 3 vertebral body segments	15	48.4	14	17.5	3	23.1	0.001
≥ 3 vertebral body segments	2	6.5	64	80.0	7	53.9	< 0.001
> 70% central cord	9	29.0	55	68.8	7	53.9	0.001
> 70% peripheral cord	6	19.4	22	27.5	3	23.1	0.423
Entire cord	2	6,5	7	8.8	2	15.4	0.692
Cord swelling	3	9.7	26	32.5	4	30.8	0.021
Cord atrophy	0	0	26	32.5	1	7.7	0.998

* Between multiple sclerosis and positive-AQP4 Neuromyelitis Optica Spectrum Disorders;
** Optic tract was evaluated from brain MRI

to have an intermediate lesion pattern between MS and NMO, was not tested due to unavailable in our institute.[10] Lastly, this study was a single-center observational study only.

In conclusion, we found that many typical MRI features, according to the NMOSD 2015 guideline, overlapped between MS and NMOSA in Thai patients. MRI features suggestive of positive-AQP4 NMOSD were LESCL, thoracic spine involvement and centrally located cord lesion. Dawson finger sign was a strongly suggestive feature of MS. AQP4-antibody testing should

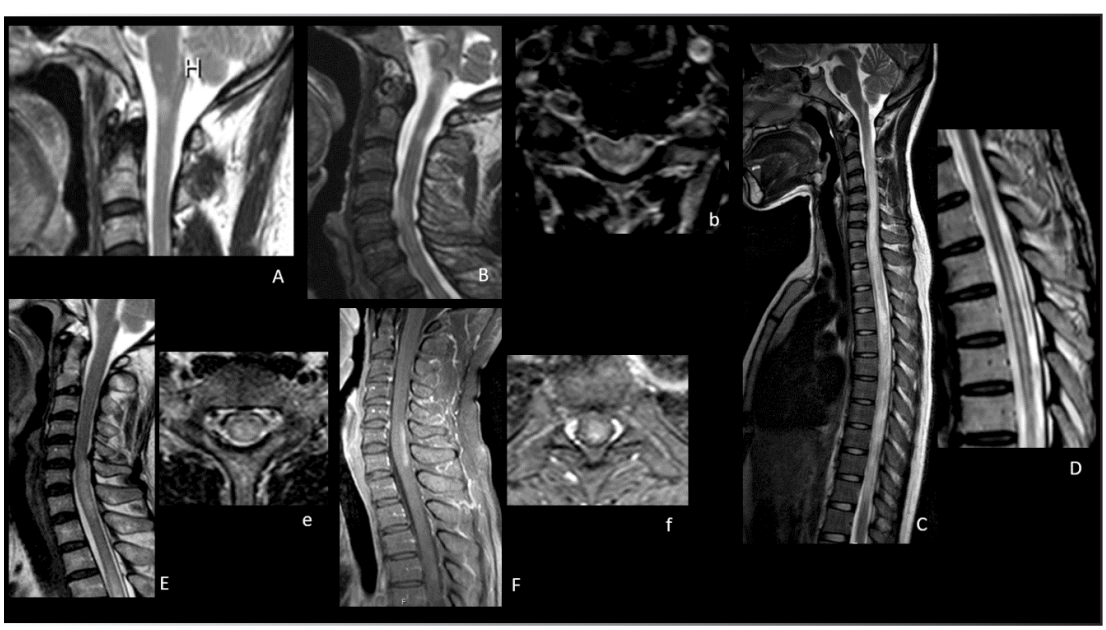

Figure 4. (A) Cervicomedullary lesion with length less than 3 vertebral body segments; (B) Cervical lesion with more than 70% peripheral involvement on axial view; (C) Involvement more than 3 vertebral body segments of the whole cord with more than 70% central involvement on axial view; (D) Spinal cord atrophy; (E, e) Lesion at cervical and thoracic levels with spinal cord edema; (F, f) Patchy enhancement on T1WI/Gd/FS on sagittal and axial views

Table 6: Adjusted odds ratio of AQP4-positive neuromyelitis optica spectrum disorders of each significant finding in brain and spinal MRI

MRI features	Adjusted OR of AQP4-positive	p-value
Dawson fingers	0.024 (0.003, 0.172)	<0.001
Thoracic-spine lesion	9.273 (1.596, 53.890)	0.013
More than 3 vertebral body segments	16.552 (2.519, 108.769)	0.003

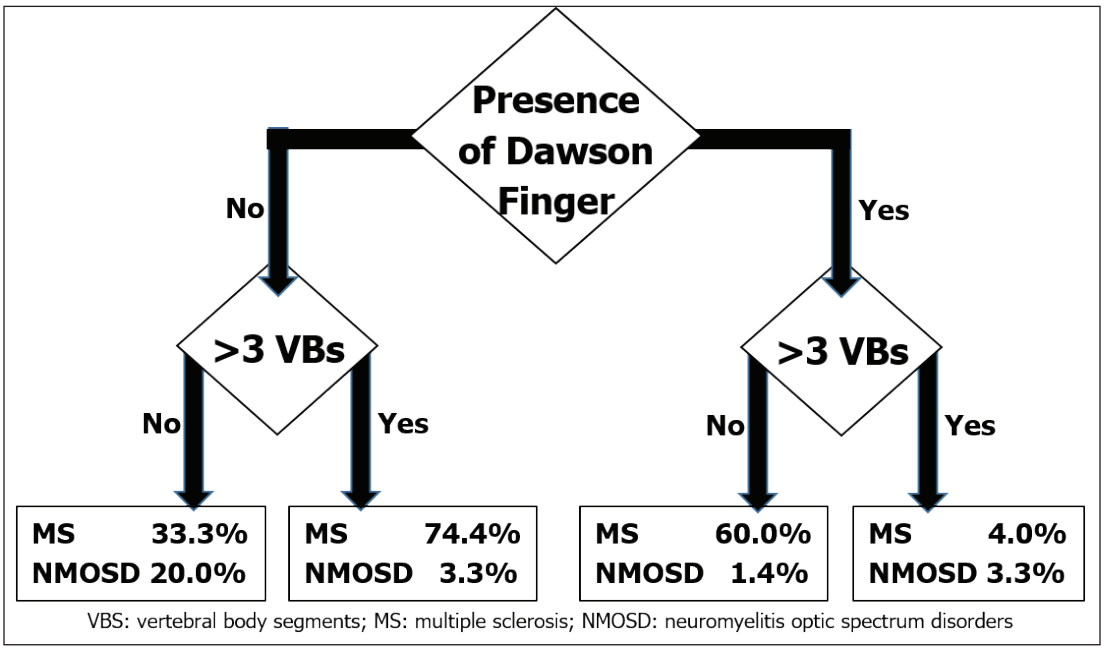

Figure 5. Algorithm in using MRI to differentiate multiple sclerosis (MS) from neuromyelitis optic spectrum disorders (NMOSD)

be performed in regions where prevalence of NMOSD is high.

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DISCLOSURE

Conflict of Interest: None

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