Multiple Sclerosis and Related Disorders 61 (2022) 103778

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Towards imaging criteria that best differentiate MS from NMOSD and MOGAD: Large multi-ethnic population and different clinical scenarios

Edgar Carnero Contentti [a,*], Juan Ignacio Rojas [b], Juan Criniti [a], Pablo A. Lopez [a], Vanessa Daccach Marques [c], Ibis Soto de Castillo [d], Verónica Tkachuk [e], Mariano Marrodan [f], Jorge Correale [f], Mauricio F. Farez [g], Ho Jin Kim [h], Jae-Won Hyun [h], Silvia Messina [i], Romina Mariano [i], Maria A. Rocca [j,k], Laura Cacciaguerra [j], Massimo Filippi [j,k,l], Jacqueline Palace [i], Maciej Juryńczyk [i,m,*]

[a] Neuroimmunology Unit, Department of Neuroscience, Hospital Alemán, Buenos Aires, Argentina
[b] Centro de Esclerosis Múltiple de Buenos Aires (CEMBA), Buenos Aires, Argentina
[c] Department of Neurosciences and Behavioral Sciences, Hospital das Clínicas, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil
[d] Neurology Department, Hospital Universitario de Maracaibo, Maracaibo, Venezuela
[e] Neuroimmunology Unit, Department of Neurology, Hospital de Clínicas "José de San Martín", Buenos Aires, Argentina
[f] Department of Neurology, Institute for Neurological Research Dr. Raúl Carrea (FLENI), Buenos Aires, Argentina
[g] Center for Research on Neuroimmunological Diseases (CIEN), Institute for Neurological Research Dr. Raúl Carrea (FLENI), Buenos Aires, Argentina
[h] Department of Neurology, Research Institute and Hospital of National Cancer Center, Goyang, South Korea
[i] Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[j] Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy
[k] Neurorehabilitation Unit and Neurophysiology Service, IRCCS San Raffaele Scientific Institute, Milan Italy
[l] Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy
[m] Laboratory of Brain Imaging, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland

ARTICLE INFO

Keywords:
Multiple sclerosis
Neuromyelitis optica spectrum disorder
Oligodendrocyte glycoprotein antibody-associated diseases

ABSTRACT

Background: The "1/3″ brain magnetic resonance imaging (MRI) criteria including 1) a lesion adjacent to the lateral ventricle and in the inferior temporal lobe, or 2) a juxtacortical lesion, or 3) a Dawson finger-type lesion were shown to distinguish multiple sclerosis (MS) from antibody-mediated conditions. In this large multicentre study, we aimed to assess how the criteria perform 1) in different onset phenotypes, 2) distinct ethnic groups, 3) when the absence of myelin oligodendrocyte glycoprotein antibody (MOG-Ab)-associated disease (MOGAD)-typical fluffy infratentorial (FIT) lesions and longitudinally extensive transverse myelitis (LETM) lesions are added as features ("2/4″ and 3/5″ criteria, respectively).

Methods: 577 patients with MS (n = 332), aquaporin-4 antibody (AQP4-Ab) neuromyelitis optica spectrum disorder (NMOSD) (n = 196) and MOGAD (n = 49) were recruited from 6 international centres (Buenos Aires, Sao Paolo, Maracaibo, Goyang, Oxford and Milan). Imaging scans were obtained at disease onset or relapse.

Results: Adding the absence of FIT lesions increased the specificity of the "1/3″ criteria vs. AQP4-Ab NMOSD from 84.7% to 87.2% and vs. MOGAD from 85.7% to 93.9% without compromising their sensitivity (86%). In particular, for those presenting with brain/brainstem attacks "2/4″ had significantly higher specificity than "1/3″ (85% vs. 80% against AQP4-Ab NMOSD, 88.9% vs. 72.2% against MOGAD). Positive predictive values of the "1/3″ criteria for MS were lowest for Asian patients (84.8 vs. 99.1% for White) but were significantly increased by adding further criteria (94.1% for "3/5″).

Conclusion: The "1/3″ criteria perform well in discriminating MS from NMOSD and MOGAD regardless of ethnic background and clinical scenario. Adding the absence of FIT lesions increases the specificity in those presenting with brain/brainstem symptoms.

* Corresponding author.
E-mail addresses: ecarnerocontentti@hospitalaleman.com (E. Carnero Contentti), m.jurynczyk@nencki.edu.pl (M. Juryńczyk).

https://doi.org/10.1016/j.msard.2022.103778
Received 6 February 2022; Received in revised form 11 March 2022; Accepted 26 March 2022
Available online 27 March 2022

1. Introduction

Although pathologically separate from each other multiple sclerosis (MS), aquaporin 4-antibody (AQP4-Ab) neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody (MOG-Ab)-associated disease (MOGAD) all present with optic neuritis, transverse myelitis and/or brain/brainstem attacks, and have overlapping paraclinical and neuroradiological features (Juryńczyk et al., 2015; Fujihara and Cook, 2020). The differential diagnosis can be challenging but making the correct ultimate diagnosis is crucial, since prognosis and treatments differ and inappropriate therapy may promote disability (Levy et al., 2021; Palace et al., 2019). AQP4-Ab and MOG-Ab assays (Waters et al., 2012; Waters et al., 2015) play a central role in the diagnosis of antibody-mediated conditions, but these are not readily available worldwide, results may take many weeks to arrive and on occasions may be borderline or inaccurate, especially with older assays (Carnero Contentti et al., 2020). In everyday clinical practice, routine brain and spinal cord magnetic resonance imaging (MRI) might be the best tool to help establish the correct diagnosis (Geraldes et al., 2018; Ciccarelli et al., 2019). Brain MRI lesion distribution criteria consisting of i) at least 1 lesion adjacent to the body of the lateral ventricle and in the inferior temporal lobe; or ii) the presence of a curved juxtacortical lesion, or iii) a Dawson's finger-type lesion, differentiate MS from NMOSD and MOGAD with high accuracy (Matthews et al., 2013; Juryńczyk et al., 2017), as validated in distinct cohorts worldwide (Bensi et al., 2018; Hyun et al., 2019; E Carnero Contentti et al., 2020; M Jurynczyk et al., 2017; Cai et al., Oct). These criteria were originally identified by comparing brain lesion probability maps in MS and AQP4-Ab NMOSD patients (Matthews et al., 2013) but were later found to also apply to MOGAD patients (Juryńczyk et al., 2017). A more recent unsupervised brain imaging analysis including patients with all three conditions showed that MOGAD patients frequently have fluffy infratentorial lesions (FIT), typically located in the brainstem or cerebellar peduncles, which are less common in AQP4-Ab NMOSD and rarely occur in MS (M Jurynczyk et al., 2017).

In this paper, we have analyzed MRI data on 577 patients obtained from 6 centres in Europe, Asia and Latin America with the aim of examining the performance of the original and modified criteria as follows:1) how adding the absence of FIT to the criteria would affect their specificity vs. AQP4-Ab NMOSD and MOGAD, 2) whether this could differ depending on the phenotype of the onset attack, 3) whether the criteria would perform better if they included the assessment of spinal cord MRI and finally 4) we investigate differences in the performance of the criteria in distinct ethnic groups.

2. Methods

2.1. Patient consents

This study was approved by the local ethics committee of each participating center and written informed consent for the use of their anonymized MRI scans for research purposes was obtained from all participants.

2.2. Patients

In this retrospective and case comparison diagnostic accuracy study, a total of 577 consecutive patients evaluated from relevant clinics were included (332 MS, 196 AQP4-Ab NMOSD and 49 MOGAD). 214 patients were recruited from Argentina (142 MS, 55 AQP4-Ab NMOSD, 17 MOGAD), 75 from Brazil (55 MS, 20 AQP4-Ab NMOSD, 0 MOGAD), 53 from Venezuela (41 MS, 12 AQP4-Ab NMOSD, 0 MOGAD), 108 from Korea (36 MS, 64 AQP4-Ab NMOSD, 8 MOGAD), 56 from Italy (32 MS, 23 AQP4-Ab NMOSD, 1 MOGAD) and 71 from United Kingdom (26 MS, 22 AQP4-Ab NMOSD, 23 MOGAD). Double-negative patients and those with an unknown status ($n = 84$) were excluded. The obtained demographic data included age, gender and ethnicity; White, Mixed (mixed white, black and American Indian ancestry), Black (including mixed white and black ancestry) and Asian (including mixed white and Asian ancestry), as described previously (Bedoya et al., 2006).

2.3. Diagnosis

The presence of AQP4- or MOG-antibodies in the serum was detected by in-house cell-based assays (CBA) in each participating center, as described previously (Waters et al., 2012; Waters et al., 2015). AQP4-Ab NMOSD was diagnosed according to the 2015 NMOSD criteria. Only NMOSD seropositive patients were included in this diagnostic category to ensure that the study findings represent the established NMOSD phenotype as closely as possible (Wingerchuk et al., 2014). MOGAD was diagnosed in patients with NMOSD seronegative or acute disseminated encephalomyelitis (including isolated brainstem attacks) associated with serum MOG antibody positivity (Jurynczyk et al., 2017; Cobo-Calvo et al., 2018) . Thus, all MOG-Ab-positive patients were negative for AQP4-Ab. MS (including clinically isolated syndromes) was diagnosed according to the 2017 revised diagnostic critera (Thompson et al., 2018). MS patients were not systematically tested for both antibodies, as the optimized AQP4-Ab and MOG-IgG1 CBA is considered highly specific for non-MS disease (Waters et al., 2012; Waters et al., 2015).

2.4. Demographic and clinical data

Each patient's medical record was reviewed locally to obtain data on age at onset, ethnicity, gender, clinical presentation and the presence of oligoclonal bands were determined by means of isoelectric focusing on cerebrospinal fluid (positivity was defined as a type II or III pattern). Onset clinical attack was classified as: 1) optic neuritis, 2) transverse myelitis, 3) optic neuritis and transverse myelitis, 4) brainstem syndrome and/or symptomatic cerebral syndrome, including cortical encephalitis with or without white matter involvement on MRI; and 5) multifocal attack involving different areas (e.g. optic neuritis and brainstem attack or optic neuritis and transverse myelitis and cerebral attack). For the purpose of analysis onset clinical attacks were then combined to form three subgroups: isolated optic neuritis, transverse myelitis (isolated or with optic neuritis), brain/brainstem attacks (with or without optic neuritis and/or transverse myelitis) based on clinical manifestations with or without involvement on MRI. Ethnic categories included: White ($n = 258$), Asian ($n = 114$), Black ($n = 4$) and Mixed ($n = 195$) ethnicity patients.

2.5. MRI and scoring

For each patient the earliest, available brain and spinal cord MRI scans performed at acute onset presentation or during a relapse were included in the study. MRI scans were acquired on 1.5 or 3.0 Tesla scanners in participating centres (Buenos Aires, Sao Pablo, Maracaibo, Goyang, Milan and Oxford) or were transferred to these centres from referring hospitals. Scanning protocols varied between centres but all of them included standard clinical sequences such as T1-weighted and T2-weighted and/or fluid-attenuated inversion recovery (FLAIR) sequences. Axial and either coronal or sagittal planes were evaluated for scoring. Slice thicknesses varied from 3 to 7 mm.

Each MRI scan was scored by two experienced raters (neurologists and/or neuroradiologists with expertise in neuroinflammatory diseases such as MS, NMOSD and MOGAD) in each participating center. The raters were blinded to the diagnosis and clinical features of patients. Consensus was reached in case of disagreement. MRI scoring included the presence of 1) a lesion adjacent to the body of the lateral ventricle and a lesion in the inferior temporal lobe, 2) a curved U-fiber juxtacortical lesion, 3) Dawson's finger-type lesion, 4) the absence of a FIT (poorly demarcated) lesion and 5) the absence of a longitudinally extensive transverse myelitis (LETM) lesion (Fig. 1) (Matthews et al., 2013; M Jurynczyk et al., 2017; Wingerchuk et al., 2014). Brain and spinal cord MRI lesion definitions are shown in **supplementary material**. After scoring had been finished, MRIs scans were

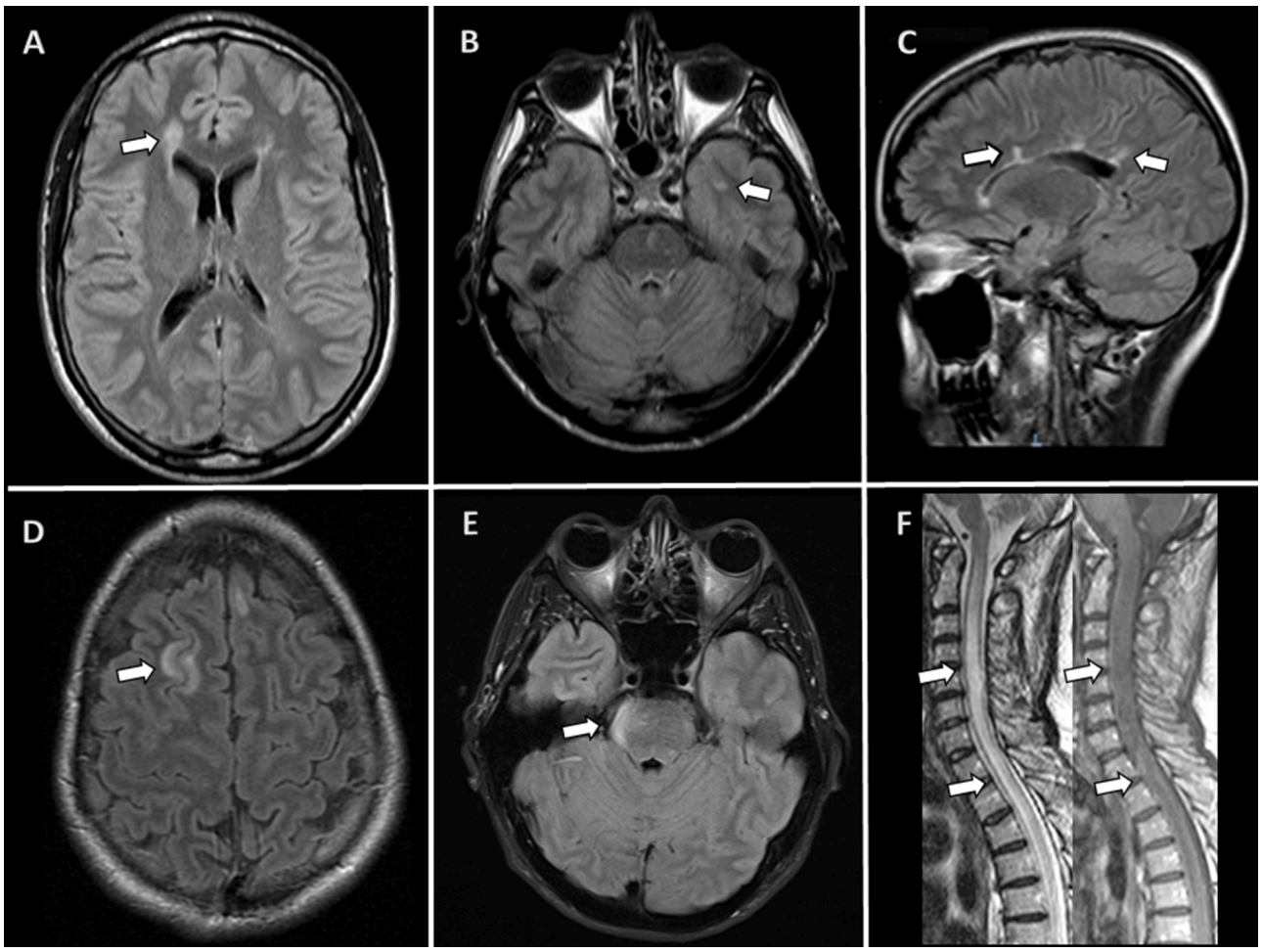

Fig. 1. Brain and spinal cord MRIs (fluid-attenuated inversion recovery sequences) from MS (A, B, C, D), MOGAD (E) and AQP4-Ab NMOSD (F) patients who fulfilled "1 out of 3" and the modified criteria. Lesions are showed with white arrows. Patients A and B had lesions adjacent to the body of a lateral ventricle and in the inferior part of the left temporal lobe, patient C had ovoid lesions perpendicular to the lateral ventricle that were compatible with Dawson's finger-type lesion, patient D had curved U-fiber juxtacortical lesions, patient E had a fluffy infratentorial (poorly demarcated) lesion and patient F had a spinal cord lesion (longitudinally extensive transverse myelitis). The absence of FIT and the absence of LETM are needed to fulfill criterion four and five, respectively.

decoded and patients were categorized according to their diagnosis: MS, AQP4-Ab NMOSD or MOGAD.

2.6. Statistical analysis

Statistical analyses were carried out using Stata v12.1 and R. Three sets of criteria were assessed: "one out of three" MS criteria as proposed by Matthews et al. (Matthews et al., 2013), "two out of four" criteria where the absence of FIT lesions was added as the fourth criterion and "three out of five" criteria where the absence of LETM lesion was added as the fifth criterion (Table 1). Logistic regression was used to assess whether age or sex are predictive for the fulfillment of distinct criteria sets. Sensitivity of the criteria was defined as the percentage of MS patients fulfilling the criteria and specificity as the percentage of non-MS patients who do not fulfill the criteria. For predictive values, we have assumed from clinical experience in participating centres and available epidemiologic data (O'Connell et al., 2020; Kim et al., 2020; Alvarenga et al., 2017) that the relative ratio of MS to MOGAD to AQP4-Ab NMOSD patients in neuroimmunology clinics is 50:2:1 in White, 1:1:1 in Asian and 5:1:1 in Mixed Latin American populations, respectively. Positive likelihood ratio (PLR) and the negative likelihood ratio (NLR), which combining sensitivity and specificity, represent a direct estimate of how much the test result changes the odds of the disease, independently on prevalence was also calculated for the entire cohort.

Receiver operating characteristics (ROC) curves were generated to assess the performance of the logistic regression model for different criteria sets with the diagnosis as the outcome variable and distinct imaging features as the explanatory variables. Area under curve (AUC) was calculated for each criteria set. Because of the exploratory nature of this study, no formal sample-size calculation was made and no adjustment for multiple testing was applied. For all the analyses, the significance level was established as $p < 0.05$.

Table 1
Magnetic resonance imaging features of the proposed sets of criteria.

Individual criteria	Sets of criteria		
A lesion adjacent to the body of lateral ventricles AND a lesion in the inferior temporal lobe A curved juxtacortical lesion A Dawson finger type lesion Absence of a fluffy infratentorial lesion Absence of an LETM lesion	"one out of three"	"two out of four"	"three out of five"

3. Results

3.1. Demographic, clinical and paraclinical features

Table 2 shows basic demographic and clinical information on the cohort. Additionally, clinical attack at presentation/relapse frequency

(**Fig. S1**) and subanalyses for pediatric patients (<18 years) are shown in **supplementary material 1 and 2**. As expected, gender distribution differed between diagnostic groups with female predominance most striking in the AQP4-Ab group (82.6% vs. 67.4% in the MS group and 57.1% in MOGAD). White patients were most prevalent in all diagnostic groups but AQP4-Ab NMOSD group contained a significant proportion of Asian patients (34% vs 11% in MS and 22% in MOGAD). ANA was more frequent in AQP4-Ab NMOSD than both MS and MOGAD. Conversely, unmatched oligoclonal bands in the CSF were significantly more common in MS (82%) than in both AQP4-Ab NMOSD (20%) and MOGAD (11%, Table 2).

Fluffy infratentorial lesions are more common in MOGAD than AQP4-antibody NMOSD.

Table 3 shows the percentage of discriminating features as scored on brain and spinal cord scans in three diagnostic groups. As expected, lesions adjacent to the body of lateral ventricles, inferior temporal lobe lesions, curved juxtacortical lesion and Dawson's finger-type lesion were significantly more frequent in MS when compared to both AQP4-Ab NMOSD and MOGAD, while LETM lesion was significantly more common in both AQP4-Ab NMOSD and MOGAD as compared with MS. FIT lesions were rare in MS and occurred more frequently in MOGAD than NMOSD (51% vs. 21%). FIT and LETM were dependent variables in MOGAD patients (86% of patients who had FIT on brain imaging also had LETM). This was not observed in AQP4-Ab NMOSD patients (50% patients with FIT also had LETM). Interestingly, in all 3 diagnostic groups Asian patients more frequently had FIT as compared with White and Mixed ethnicity patients (Table 4). There were no gender differences in the prevalence of FIT lesions in any diagnostic group (data not shown).

116/195 (59.1%) AQP4-Ab NMOSD, 23/49 (46.9%) MOGAD and 9/322 (2.7%) MS patients showed the presence of an LETM lesion on spinal cord imaging (Table 3).

Table 2
Basic demographic and clinical information about the patients included in the study.

Characteristics	MS	AQP4-Ab NMOSD	MOGAD	P-value[a]	P-value[b]
N	332	196	49		
Mean age at onset, years, (range)	32 (10-67)	38 (2-79)	23 (2-49)	<0.0001	<0.0001
Female (%)	224 (67.4)	162 (83)	28 (57)	0.0002	0.19
Latin America	238 (71.6)	87 (44.3)	17 (34.6)	<0.0001	<0.0001
Argentina (Buenos Aires)	142 (42.8)	55 (28.1)	17 (34.6)		
Brazil (Sao Paolo)	55 (16.6)	20 (10.2)	0		
Venezuela (Maracaibo)	41 (12.3)	12 (6.1)	0		
South Korea (Goyang)	36 (10.8)	64 (32.6)	8 (16.2)	<0.0001	0.33
UK (Oxford)	26 (7.8)	22 (11.2)	23 (46.9)	0.21	<0.0001
Italy (Milan)	32 (9.6)	23 (11.7)	1 (2.1)	0.46	0.10
Ethnicity					
White	162 (49)	72 (37)	24 (49)	0.008	1
Black	4 (1)	6 (3)	0	0.18	1
Mixed	130 (39)	51 (26)	14 (39)	0.002	0.20
Asian	26 (11)	67 (34)	11 (22)	<0.0001	0.003
Paraclinical features					
Serum antinuclear antibodies (%)	31/192 (16.1)	31/123 (25.2)	2/19	0.054	0.74
CSF unmatched oligoclonal bands (%)	161/196 (82)	21/105 (20)	(10.5) 4/36 (11)	<0.0001	<0.0001

[a] MS vs. AQP4-Ab NMOSD results were compared.
[b] MS vs. MOGAD results were compared.

"One out of three" criteria show high sensitivity and specificity when differentiating MS from both AQP4-Ab NMOSD and MOGAD.

A total of 286 (86.1%) MS patients fulfilled the "one out of three" MS criteria (Table 5) at acute attack as compared with 30 (15.3%) AQP4-Ab NMOSD and 7 (14.3%) MOGAD patients. This resulted in 86.1% sensitivity for the diagnosis of MS and 84.7% specificity vs. AQP4-Ab NMOSD and 85.7% vs. MOGAD. Asian MS patients had lower sensitivity for MS (75%) but similar specificity vs. AQP4-Ab NMOSD (86.6%) and greater vs. MOGAD (100%) when compared with other ethnic groups (Table 5). This was due to Asian patients less frequently having Dawson's finger type and curved juxtacortical lesions (64 and 22%, respectively) as compared with White (72% and 53%, respectively) or Mixed (76% and 58%) ethnicities. Interestingly, in the MOGAD group females more frequently fulfilled the criteria as compared with males (21.4 vs. 4.8%, respectively). Age influenced the probability of fulfilling the "one out of three criteria" only in the MOGAD group (logistic regression, $p<0.05$) with younger patients more likely to fulfill the criteria as compared with older ones (20.7% patients before the age of 30 years vs. 5% in 30 years old or older). Sex did not affect the chance to fulfill the criteria in any diagnostic group.

Proportions of patients fulfilling different sets of criteria in the total cohort and in ethnic groups.

The absence of FIT on the brain MRI increases the specificity of the criteria without compromising their sensitivity.

When the absence of FIT was added as the fourth criterion the "two out of four" criteria retained high sensitivity (85.8%) of the "one out of three" criteria but had better specificity, in particular vs. MOGAD (93.9%, Table 5). For the discrimination of MS vs. MOGAD including the absence of FIT in the criteria increased the area under ROC curve from 0.84 to 0.94 (Fig. 2)

Adding the absence of LETM slightly increases the specificity of the criteria to diagnose MS vs. *AQP4-Ab NMOSD but does not affect specificity* vs. *MOGAD.*

Adding the absence of LETM to the criteria increased their specificity to 91.8% vs. AQP4-Ab NMOSD and maintained the high specificity of the "two out of four" criteria vs. MOGAD (93.9%). Fig. 2 shows how adding the absence of LETM to the "2/4″ criteria increases the ability of the criteria to discriminate MS from AQP4-Ab NMOSD, but not MOGAD.

Table 3
Brain and spinal cord MRI findings in three diagnostic groups.

MRI feature	MS	AQP4-Ab NMOSD	MOGAD	P-value*
≥ 1 lesion adjacent to lateral ventricle (%)	310 (93.3)	53 (27.1)	9 (18.3)	<0.0001
≥ 1 lesion in the inferior temporal lobe (%)	176 (53)	18 (9)	5 (10)	<0.0001
≥ 1 lesion adjacent to lateral ventricle (%) AND ≥ 1 in the inferior temporal lobe (%)	170 (51)	11 (6)	3 (6)	<0.0001
≥ 1 juxtacortical lesions (%)	173 (52.1)	16 (8.1)	7 (14.2)	<0.0001
≥ 1 Dawson's finger (%)	242 (72.8)	14 (7.1)	1 (2.1)	<0.0001
≥ 1 FIT lesion (%)	14 (4.2)	41 (20.9)	25 (51.1)	<0.0001
LETM lesion	9/332 (2.7)	116/195 (59.1)	23/49 (46.9)	<0.0001

* These values correspond to: MS vs. AQP4-Ab NMOSD and MS vs. MOGAD.

Table 4
Presence of fluffy infratentorial lesions (poorly demarcated) according to ethnicity.

	MS	AQP4-Ab NMOSD	MOGAD	P-value[a]	P-value[b]
FIT lesions, N (%)					
White	6/162 (4)	6/72 (8)	13/24 (54)	0.19	<0.0001
Asian	7/36 (19)	31/67 (46)	8/11 (73)	0.009	0.001
Mixed	1/130 (1)	3/51 (6)	4/14 (29)	0.06	0.0002

[a] MS vs. AQP4-Ab NMOSD results were compared.
[b] MS vs. MOGAD results were compared.

Table 5
Number of patients fulfilling the criteria and evaluation of each sets of criteria according to ethnicity for the discrimination between MS and from both antibody-mediated conditions.

	1/3	2/4	3/5
Total cohort			
MS patients (%)	286 (86.1)	285 (85.8)	274/332 (85.1)
NMOSD patients (%)	30 (15.3)	25 (12.8)	16/195 (8.2)
MOGAD patients (%)	7 (14.3)	3 (6.1)	3/49 (6.1)
Sensitivity	86.1%	85.8%	85.1%
Specificity vs. AQP4-Ab NMOSD	84.7%	87.2%	91.8%
Specificity vs. MOGAD	85.7%	93.9%	93.9%
Positive likelihood ratio	5.70	7.51	10.64
Negative likelihood ratio	0.16	0.16	0.19
Accuracy	85.6%	87%	88.2%
White patients			
MS	137/162 (84.6)	137 (84.6)	126/152 (82.9)
NMOSD	12/72 (16.7)	11 (15.3)	8/72 (11.1)
MOGAD patients	3/24 (12.5)	1 (4.2)	1/24 (4.2)
Sensitivity	84.6%	84.6%	82.9%
Specificity vs. AQP4-Ab NMOSD	83.3%	84.7%	88.9%
Specificity vs. MOGAD	87.5%	95.8%	95.8%
Accuracy	84.7%	85.9%	85.9%
Positive predictive value	99.1%	99.4%	99.5%
Negative predictive value	25.2%	26.3%	24.7%
Asian patients			
MS	27/36 (75)	26 (72.2)	26/36 (72.2)
NMOSD	9/67 (13.4)	6 (9)	3/66 (4.5)
MOGAD patients	0/11	0	0/11
Sensitivity	75%	72.2%	72.2%
Specificity vs. AQP4-Ab NMOSD	86.6%	91%	95.5%
Specificity vs. MOGAD	100%	100%	100%
Accuracy	84.1%	85.8%	88.5%
Positive predictive value	84.8%	88.9%	94.1%
Negative predictive value	88.2%	87.3%	87.6%
Mixed ethnicity			
MS	118/130 (90.8)	118 (90.8)	118/130 (90.8)
NMOSD	7/51 (13.7)	6 (11.8)	5/51 (9.8)
MOGAD patients	4/14 (28.6)	2 (14.3)	2/14 (14.3)
Sensitivity	90.8%	90.8%	90.8%
Specificity vs. AQP4-Ab NMOSD	86.3%	88.2%	90.2%
Specificity vs. MOGAD	71.4%	85.7%	85.7%
Accuracy	88.2%	89.7%	90.3%
Positive predictive value	91.5%	94.5%	94.9%
Negative predictive value	77.5%	79%	79.2%

Table 6
Performance of the proposed MRI diagnostic criteria depending on the phenotype of a clinical attack.

	1/3	2/4	3/5
Optic neuritis onset			
MS	63/72 (87.5)	63 (87.5)	63/72 (87.5)
AQP4-Ab NMOSD	11/66 (16.7)	9 (13.6)	8/65 (12.3)
MOGAD	2/19 (10.5)	1 (5.3)	1/19 (5.3)
Sensitivity	87.5%	87.5%	87.5%
Specificity NMOSD	83.3%	86.4%	87.7%
Specificity MOGAD	89.5%	94.7%	94.7%
Accuracy	86.3%	88.6%	89.2%
Transverse myelitis onset			
MS	103/125 (82.4)	103 (82.4)	102/125 (81.6)
AQP4-Ab NMOSD	11/90 (12.2)	10 (11.1)	7/90 (7.8)
MOGAD	0/12 (0)	0	0
Sensitivity	82.4%	82.4%	81.6%
Specificity NMOSD	87.8%	88.9%	92.2%
Specificity MOGAD	100%	100%	100%
Accuracy	86.1%	86.5%	87.3%
Brain/brainstem onset			
MS	118/133 (88.7%)	117 (88)	109/125 (87.2)
AQP4-Ab NMOSD	8/40 (20)	6 (15)	1/40 (2.5)
MOGAD	5/18 (27.8)	2 (11.1)	2/18 (11.1)
Sensitivity	88.7%	88%	87.2%
Specificity NMOSD	80%	85%	97.5%
Specificity MOGAD	72.2%	88.9%	88.9%
Accuracy	86.2%	88.2%	90.3%

Information on the onset attack in two MS patients was not available.

4. Performance of the proposed MRI diagnostic criteria depending on the phenotype of a clinical attack (Table 6)

4.1. Patients presenting with isolated optic neuritis

63/72 (87.5%) MS, 11/66 (16.7%) AQP4-Ab NMOSD and 2/19 (10.5%) MOGAD patients presenting with optic neuritis fulfilled "one out of three" criteria. Among those with optic neuritis onset three (4.2%) MS, five (7.6%) AQP4-Ab NMOSD and six (31.6%) MOGAD patients had FIT lesions on the scored images. Adding the absence of FIT lesions to the criteria left sensitivity unchanged (87.5%) but increased their specificity vs. AQP4-Ab NMOSD from 83.3% to 86.4% and vs. MOGAD from 89.5% to 94.7%. Adding the absence of LETM did not influence further neither sensitivity nor specificity of the criteria in patients with optic neuritis onset.

4.2. Patients presenting with transverse myelitis onset (with or without optic neuritis)

Among those presenting with transverse myelitis 103 (82.4%) MS, 11 (12.2%) AQP4-Ab NMOSD and none of MOG-Ab patients fulfilled the "one out of three" criteria. One (0.8%) MS, 14 (15.6%) AQP4-Ab NMOSD and four (33.3%) MOGAD patients were scored to have FIT lesions. Adding the absence of FIT lesions increased the specificity of the criteria vs. AQP4-Ab NMOSD from 87.8 to 88.9%, while specificity vs. MOGAD remained 100%. The percentage of LETM was 4.8% in the MS group, 78.9% in AQP4-Ab NMOSD and 75% in MOGAD. Including the absence of LETM in the "three out of five" criteria increased their specificity vs. AQP4-Ab NMOSD to 92.2%.

4.3. Patients presenting with brain/brainstem onset

Among those presenting with brain/brainstem attacks (with or without optic neuritis or transverse myelitis) 118 (88.7%) MS, 8 AQP4-Ab NMOSD (20%) and 5 (27.8%) MOGAD patients fulfilled the "one out

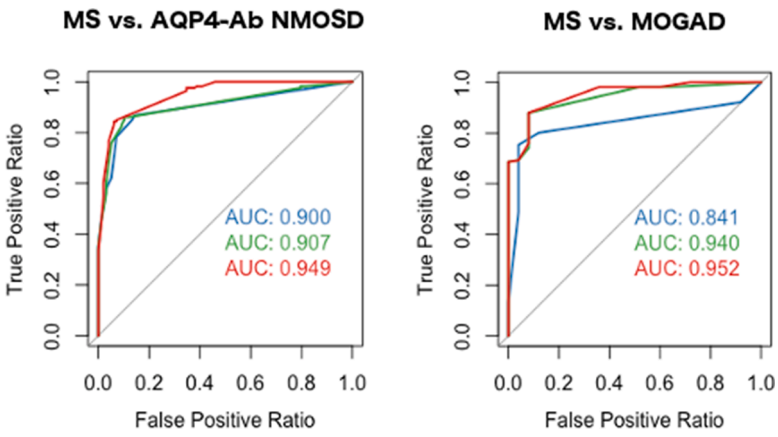

Fig. 2. Performance of the binary classifier is graphically shown as area under ROC curve. **Blue** - only the 3 original criteria are included in the logistic model, **green** - the absence of FIT is added as the fourth variable, **red** - the absence of LETM is added as the fifth variable.

of three" criteria. FIT lesions were found in 10 (7.5%) MS, 22 (55%) AQP4-Ab NMOSD and 15 (83.3%) MOGAD patients. Adding the absence of FIT lesions to the criteria increased their specificity vs. AQP4-Ab NMOSD from 80% to 85% and vs. MOGAD from 72.2% to 88.9%. Adding the absence of LETM lesions to the criteria increased their specificity vs. AQP4-Ab NMOSD (97.5%), maintaining their specificity vs. MOGAD (88.9%).

5. Discussion

In this study using clinical practice conventional MRIs, obtained from different countries and centres, from patients in different clinical scenarios at presentation or during a relapse, we confirmed that the "one out of three" criteria (Matthews et al., 2013) were able to correctly differentiate MS from both AQP4-Ab NMOSD and MOGAD in the vast majority of cases. In terms of specificity the "one out of three" criteria performed better in those with optic neuritis or transverse myelitis onset (83–100%) as compared with patients presenting with brain/brainstem attacks (80% vs. NMOSD and 72% vs. MOGAD). Interestingly, adding the absence of FIT lesions as the fourth criterion increased the specificity of criteria without compromising their sensitivity and this also applied when the initial attack involved the brain/brainstem (85% specificity vs. NMOSD, 89% vs. MOGAD). Adding spinal cord imaging allowing for the assessment of LETM retained or slightly increased the accuracy of the criteria. The criteria performed well not only in different clinical scenarios but also regardless of the patient's ethnic background. Although the sensitivity was moderate in Asian patients (72–75%) it was accompanied by highest specificity (87–100%). Interestingly, Asian patients more often had FIT lesions, in particular in antibody-mediated groups.

Our study examined the significance of FIT lesions for the diagnosis not only because these lesions are frequently reported in MOGAD but also because they might accompany an LETM lesion (Jarius et al., 2016). Indeed, in this study FIT lesions co-existed with LETM in 54% cases. Of note, FIT lesions can be assessed if spinal cord imaging is not available. Interestingly when FIT lesions are already included in the criteria the added value of LETM is limited. Importantly the criteria including FIT lesions should ideally be applied in the acute attack as these lesions typically resolve on follow-up imaging (M Jurynczyk et al., 2017; Kitley et al., 2014). Evolution of lesions in time also applies to LETM lesions (Asgari et al., 2013). As the modified criteria are however based on the original "one out of three" criteria they will show performance identical to "one out of three" criteria if applied in remission (absence of FIT lesions counting as one criterion in "two out of four" regardless of diagnostic group).

Assessing the performance of criteria in different populations worldwide is an important strength of this project. MS is significantly more prevalent than NMOSD in white populations, while NMOSD predominates in Asian and Black patients (Wingerchuk et al., 2007). Patients of non-white background such as Afro-Brazilians were also over-represented in NMOSD studies in Latin America (Papais-Alvarenga et al., 2002). Predisposition to MOGAD does not appear to be influenced by ethnicity but this warrants further studies (Jurynczyk et al., 2017). Taking into account these differences it was interesting to examine how the criteria perform in various ethnic settings. The importance of the criteria for the ultimate diagnosis will also rise in underprivileged areas where access to optimized antibody assays is limited as well as in case of low-positive MOG antibody results which can be non-specific (Reindl et al., 2020). We have found that the criteria show satisfactory sensitivity and specificity in all ethnic groups including White, Asian and mixed ethnicity patients. The criteria were least sensitive for Asian MS patients but still a vast majority of them fulfilled them. This might be in line with a previous study showing that Japanese patients with MS had a trend towards fewer T2-weighted lesions as compared with White patients (Nakamura et al., 2018). Importantly features included in the criteria were exceptional in non-MS patients leading to their high specificity. Another interesting finding was that FIT lesions were more frequently observed in Asian patients than other ethnic groups regardless of the diagnostic group. Including additional features in the criteria added most value in Asian patients as shown by the positive predictive value for the diagnosis of MS increasing from 84.8 to 94.1% (latter for "three out of five").

This study has several limitations. First, it was a retrospective study, findings should be interpreted with caution, since unintentional selection bias may have occurred given the relatively small numbers of patients included in the MOGAD subgroup. Patients' numbers in each diagnostic group might not reflect the real prevalence of these conditions in the neuroinflammatory clinic. Additionally, these findings were not evaluated in seronegative NMOSD patients. Second, MRIs from acute attack were typically but not always obtained from the first onset attack, which should be taken into account when interpreting the performance of the criteria in distinct onset phenotypes. Thus, heterogeneity of cohorts and patients' groups unbalanced should be consider as an important limitation. However, these limitations show its real-world applicability in clinical practice. Thirdly, most Asian patients come from one single center and the number of Black patients is low. Still this is to our knowledge the largest and most diverse study to date assessing the performance of imaging criteria to differentiate MS from non-MS antibody-mediated conditions. Another limitations is that our study did not assess other potentially useful features such as cortical lesions or periependymal lesions along lateral ventricles which were shown to be potentially useful in another study optimizing criteria to distinguish MS from NMOSD (Cacciaguerra et al., 2019). We have not included cortical lesions as the sensitivity of routine scans is low (5–9%) for this feature and rises only to below 25% even with most advanced techniques at 3

Tesla (Bouman et al., 2020) . Furthermore, our experience with linear peripendymal lesions is that they might be difficult to distinguish from non-specific symmetric linear hyperintensities abutting the lateral ventricles (Filippi et al., 2019).

In summary, in this large and multicentre study we have shown that "one out of three" brain imaging criteria are able to distinguish MS from both AQP4-antibody NMOSD and MOGAD regardless of patient's ethnic background and onset presentation. Adding the fourth criterion which can be assessed on brain imaging in the acute phase of the attack increases the performance of the criteria further in particular in patients presenting with brain/brainstem attacks. Further studies are needed to clarify whether including brainstem criterion could be a surrogate for the presence of LETM on spinal cord imaging.

Author contributions

ECC, JP and MJ contributed to the conception and design of the study. All authors contributed to the acquisition and analysis of data. ECC, JIR, JC, JP and MJ contributed to drafting the text, statistical analyses and preparing the figures. All authors contributed to revising the manuscript for intellectual content. All authors approved the final version of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

Hyun has received a grant from the National Research Foundation of Korea. Juryńczyk receives funding from National Agency For Academic Exchange "Polish Returns" program (PPN/PPO/2020/1/00043/U/00001). The rest of the authors have not conflict of interests relating to this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.103778.

References

Asgari, N., Skejoe, H.P.B., Lillevang, S.T., et al., 2013. Modifications of longitudinally extensive transverse myelitis and brainstem lesions in the course of neuromyelitis optica (NMO): a population-based, descriptive study [Internet] BMC Neurol. 13 (1), 33 [cited 2018 Jun 6] Available from: http://www.ncbi.nlm.nih.gov/pubmed/23566260.

Alvarenga, M.P., Schimidt, S., Alvarenga, R.P., 2017. Epidemiology of neuromyelitis optica in Latin America. Mult. Scler. J. - Exp. Transl. Clin. 3 (3), 2055217317730098.

Bensi, C., Marrodan, M., González, A., et al., 2018. Brain and spinal cord lesion criteria distinguishes AQP4-positive neuromyelitis optica and MOG-positive disease from multiple sclerosis. Mult. Scler. Relat. Disord. 25, 246–250.

Bedoya, G., Montoya, P., García, J., et al., 2006. Admixture dynamics in Hispanics: a shift in the nuclear genetic ancestry of a South American population isolate. Proc. Natl. Acad. Sci. U. S. A. 103 (19), 7234–7239.

Bouman, P.M., Steenwijk, M.D., Pouwels, P.J.W., et al., 2020. Histopathology-validated recommendations for cortical lesion imaging in multiple sclerosis. Brain 143 (10), 2988–2997.

Carnero Contentti, E., Rojas, J.I., Cristiano, E., et al., 2020a. Latin American consensus recommendations for management and treatment of neuromyelitis optica spectrum disorders in clinical practice. Mult. Scler. Relat. Disord. 45, 102428.

Ciccarelli, O., Cohen, J.A., Reingold, S.C., et al., 2019. Spinal cord involvement in multiple sclerosis and neuromyelitis optica spectrum disorders. Lancet Neurol. 18 (2), 185–197.

Carnero Contentti, E., Marques, V.D., Soto de Castillo, I., et al., 2020b. Brain and spinal MRI features distinguishing MS from different AQP4 antibody serostatus NMOSD at disease onset in a cohort of Latin American patients. Mult. Scler. J. 26 (8), 945–954.

Cai, M.T., Zhang, Y.X., Zheng, Y., Yang, F., Fang, W., Shen, C.H., 2019 Oct. Ding MP. Brain lesion distribution criteria distinguish demyelinating diseases in China. Ann. Clin. Transl. Neurol. 6 (10), 2048–2053.

Cobo-Calvo, A., Ruiz, A., Maillart, E., et al., 2018. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: the MOGADOR study. Neurology 90 (21), e1858–e1869.

Cacciaguerra, L., Meani, A., Mesaros, S., et al., 2019. Brain and cord imaging features in neuromyelitis optica spectrum disorders. Ann. Neurol. 85 (3), 371–384.

Fujihara, K., Cook, L.J., 2020. Neuromyelitis optica spectrum disorders and myelin oligodendrocyte glycoprotein antibody-associated disease: current topics. Curr. Opin. Neurol. 33 (3), 300–308.

Filippi, M., Preziosa, P., Banwell, B.L., et al., 2019. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain 142 (7), 1858–1875.

Geraldes, R., Ciccarelli, O., Barkhof, F., et al., 2018. The current role of MRI in differentiating multiple sclerosis from its imaging mimics. Nat. Rev. Neurol. 14 (4), 199–213.

Hyun, J.W., Huh, S.Y., Shin, H.J., et al., 2019. Evaluation of brain lesion distribution criteria at disease onset in differentiating MS from NMOSD and MOG-IgG-associated encephalomyelitis. Mult. Scler. J. 25 (4), 585–590.

Juryńczyk, M., Craner, M., Palace, J., 2015. Overlapping CNS inflammatory diseases: differentiating features of NMO and MS. J. Neurol. Neurosurg. Psychiatry 86 (1), 20–25.

Juryńczyk, M., Tackley, G., Kong, Y., et al., 2017. Brain lesion distribution criteria distinguish MS from AQP4-antibody NMOSD and MOG-antibody disease. J. Neurol. Neurosurg. Psychiatry 88 (2).

Jurynczyk, M., Geraldes, R., Probert, F., et al., 2017a. Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis. Brain 140 (3), 617–627.

Jurynczyk, M., Messina, S., Woodhall, M.R., et al., 2017b. Clinical presentation and prognosis in MOG-antibody disease: a UK study. Brain 140 (12), 3128–3138.

Jarius, S., Kleiter, I., Ruprecht, K., et al., 2016. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 3: brainstem involvement - frequency, presentation and outcome. J. Neuroinflammation 13 (1).

Kitley, J., Waters, P., Woodhall, M., et al., 2014. Neuromyelitis Optica Spectrum Disorders With Aquaporin-4 and Myelin-Oligodendrocyte Glycoprotein Antibodies: a Comparative Study [Internet]. JAMA Neurol. 1–8 [cited 2014 Feb 22] Available from: http://www.ncbi.nlm.nih.gov/pubmed/24425068.

Kim, J.E., Park, S.H., Han, K., et al., 2020. Prevalence and incidence of neuromyelitis optica spectrum disorder and multiple sclerosis in Korea. Mult. Scler. J. 26 (14), 1837–1844.

Levy, M., Fujihara, K., Palace, J., 2021. New therapies for neuromyelitis optica spectrum disorder. Lancet Neurol. 20 (1), 60–67.

Matthews, L., Marasco, R., Jenkinson, M., et al., 2013. Distinction of seropositive NMO spectrum disorder and MS brain lesion distribution. Neurology 81 (22), 1966.

Nakamura, Y., Gaetano, L., Matsushita, T., et al., 2018. A comparison of brain magnetic resonance imaging lesions in multiple sclerosis by race with reference to disability progression. J. Neuroinflammation 15 (1), 255.

O'Connell, K., Hamilton-Shield, A., Woodhall, M., et al., 2020. Prevalence and incidence of neuromyelitis optica spectrum disorder, aquaporin-4 antibody-positive NMOSD and MOG antibody-positive disease in Oxfordshire. UK. J. Neurol. Neurosurg. Psychiatry 91 (10), 1126–1128.

Palace, J., Lin, D.Y., Zeng, D., et al., 2019. Outcome prediction models in AQP4-IgG positive neuromyelitis optica spectrum disorders. Brain 142 (5), 1310–1323.

Papais-Alvarenga, R.M., Miranda-Santos, C.M., Puccioni-Sohler, M., et al., 2002. Optic neuromyelitis syndrome in Brazilian patients. J. Neurol. Neurosurg. Psychiatry 73 (4), 429–435.

Reindl, M., Schanda, K., Woodhall, M., et al., 2020. International multicenter examination of MOG antibody assays. Neurol. Neuroimmunol. Neuroinflammation 7 (2).

Thompson, A.J., Banwell, B.L., Barkhof, F., et al., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17 (2), 162–173.

Waters, P.J., McKeon, A., Leite, M.I., et al., 2012. Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays [Internet]. Neurology 78 (9), 665–671. discussion 669. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3286228&tool=pmcentrez&rendertype=abstract.

Waters, P., Woodhall, M., O'Connor, K.C.K.C., et al., 2015. MOG cell-based assay detects non-MS patients with inflammatory neurologic disease. Neurol. Neuroimmunol. Neuroinflammation 2 (3), e89.

Wingerchuk, D., Banwell, B., Bennett, J., et al., 2014. Revised Diagnostic Criteria for Neuromyeltiis Optica Spectrum Disorders. Neurology 82 (10). Supplement S63.001.

Wingerchuk, D.M., Lennon, V.A., Lucchinetti, C.F., et al., 2007. The spectrum of neuromyelitis optica. Lancet Neurol. 6 (9), 805–815.