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Appendix S1

Co-Investigators/Affiliated Members of The Guthy-Jackson Charitable Foundation

International Clinical Consortium (GJCF-ICC): Raed Alroughani, MD, Amiri Hospital, Kuwait City, Kuwait; Metha Apiwattanakul, MD, Neurological Institute of Thailand, Bangkok, Thailand; Georgina Arrambide, MD, PhD, Cemcat, Vall d'Hebron University Hospital, Barcelona, Spain; Jagannadha Avasarala, MD, PhD, University of Kentucky Medical Center, Lexington, KY, USA; Alexey Boyko, MD, PhD, Pirogov Russian Scientific and Research University, Federal Center of Brain Research and Neurotechnologies, Moscow MS Center, Moscow, Russia; Edgar Carnero Contentti, MD, MSc, Neuroimmunology Unit, Neurosciences Department, Hospital Aleman, Buenos Aires, Argentina; Alvaro Cobo-Calvo, MD, PhD, Multiple Sclerosis Centre of Catalonia (Cemcat), Barcelona, Spain; Guillermo Delgado-Garcia, MD, MSc, University of Calgary, Calgary, Canada; Jose Flores, MD, MSc, National University of México/ABC Neurological Center, México City, Mexico; May Han, MD, Stanford, Stanford, CA, USA; Jyh Yung Hor, MD, Penang General Hospital, Penang, Malaysia; Saif Huda, MD, DPhil, Walton Centre NHS Foundation Trust, Liverpool, United Kingdom; Raffaele Iorio, MD, PhD, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; Anu Jacob, MD, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates; Maciej Juryńczyk, MD, PhD, Laboratory of Brain Imaging, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland; Ingo Kleiter, MD, Marianne-Strauß-Klinik, Behandlungszentrum Kempfenhausen für Multiple Sklerose Kranke gGmbH, Berg, Germany; Marco Lana-Peixoto, MD, PhD, Federal University of Minas Gerais, Belo Horizonte, Brazil; Michael Levy, MD, PhD, Massachusetts General Hospital, Boston, MA, USA; Romain Marignier, MD, Lyon University Hospital, Lyon, France; Sara Mariotto, MD, PhD, Neurology Unit, Department of Neurosciences, Biomedicine, and Movement Sciences, University of Verona, Verona, Italy; Esther Melamed, MD, PhD, Dell Medical School, Austin, TX, USA; Ichiro Nakashima, MD, PhD, Tohoku Medical and Pharmaceutical University, Sendai, Japan; Veronika E. Neubrand, PhD, University of Granada, Granada, Spain; Celia Oreja-Guevara, MD, PhD, Hospital Clinico San Carlos, Madrid, Spain; Jacqueline Palace, BM, FRCP, DM, Oxford University, Oxford, United Kingdom; Renata Barbosa Paolilo, MD, PhD, University of São Paulo, São Paulo, Brazil; Anne-Katrin Pröbstel, MD, PhD, University of Basel, Basel, Switzerland; Chao Quan, MD, PhD, Department of Neurology, National Center for Neurological Disorders, Huashan Hospital, Fudan University, Shanghai, China; Pavle Repovic, MD, PhD, Swedish Medical Center, Seattle, WA, USA; Claire S. Riley, MD, Columbia University Medical Center, New York, NY, USA; Juan I. Rojas, MD, Hospital Universitario de CEMIC, Buenos Aires, Argentina, Buenos Aires, Argentina; Klemens Ruprecht, MD, Charité - Universitätsmedizin Berlin, Berlin, Germany; Albert Saiz, MD, PhD, Hospital Clinic de Barcelona, IDIBAPS, and University of Barcelona, Barcelona, Spain; Che Serguera, MD, PhD, INSERM, Paris, France; Ibis Soto de Castillo, MD, Hospital Universitario de Maracaibo, Maracaibo, Venezuela; Pablo Villoslada, MD, Stanford, Stanford, CA, USA; Barbara Willekens, MD, PhD, Antwerp University Hospital and University of Antwerp, Edegem, Belgium; Dean Wingerchuk, MD, Mayo Clinic, Scottsdale, AZ, USA; Bassem Yamout, MD, FAAN, Harley Street Medical Center, Abu Dhabi, United Arab Emirates.

Table S1 | Literature search in PubMed for search terms “[prevalence] OR [MRI] OR [multicentre] AND [NMOSD]” from database inception to February 6, 2024.

PMID	Publication Year	Comments	Type of Study
22733096	2012	*	population
22551731	2012	*	prognostic
22491862	2012	pregnancy symptoms focused	pregnancy
22260418	2012	*	population
23407702	2013	MS focused	MS
		no information on types of attacks or	
23076828	2013	MRI lesion locations	prognostic
23566260	2013	*	MRI
		no information on types of attacks or	
25199960	2014	MRI lesion locations	prognostic
		no information on types of attacks or	
24647557	2014	MRI lesion locations	prognostic
24323817	2014	*	prognostic
		no information on types of attacks or	
26222205	2015	MRI lesion locations	population
25965287	2015	*	population
			MOG-AD &
27802825	2016	MOG-AD focused	pediatric
27793206	2016	MOG-AD focused	MOG-AD
		no information on types of attacks or	
26810718	2016	MRI lesion locations	prognostic
		no information on types of attacks or	
27113605	2016	MRI lesion locations	diagnostic
29093070	2017	pregnancy symptoms only	pregnancy
29063242	2017	MOG-AD focused	MOG-AD
28768844	2017	MOG-AD focused	MOG-AD
		no information on types of attacks or	
28572277	2017	MRI lesion locations	prognostic

		no information on types of attacks or	
28131216	2017	MRI lesion locations	prognostic
28058965	2017	*	population
28017203	2017	pregnancy symptoms focused	pregnancy
27951522	2017	*	MRI
		no information on types of attacks or	
27783452	2017	MRI lesion locations	prognostic
28451627	2017	*	population
		no information on types of attacks or	
30413632	2018	MRI lesion locations	population
			MOG-AD &
30212767	2018	MOG-AD focused	pediatric
30056361	2018	*	population
		no information on types of attacks or	
30015079	2018	MRI lesion locations	population
29789706	2018	*	MRI
29156226	2018	*	MRI
		no information on types of attacks or	
31495497	2019	MRI lesion locations	clinical trial
31471461	2019	*	diagnostic
31016376	2019	*	MRI
30623860	2019	pediatric patients only	pediatric
		no information on types of attacks or	
31610404	2019	MRI lesion locations	prognostic
		no information on types of attacks or	
33147540	2020	MRI lesion locations	prognostic
33032052	2020	*	MRI
32898832	2020	*	MRI
		no information on types of attacks or	
32683306	2020	MRI lesion locations	SARS CoV-2

		no information on types of attacks or	
32333898	2020	MRI lesion locations	clinical trial
32333897	2020	*	clinical trial
32199095	2020	*	clinical trial
31982662	2020	*	prognostic
31706167	2020	*	diagnostic
31124748	2020	*	MRI
31877445	2020	*	prognostic
33122310	2020	*CROCTINO	population
34213614	2021	*	population
		no information on types of attacks or	
33724534	2021	MRI lesion locations	exploratory
33279797	2021	*	population
		no information on types of attacks or	
33103295	2021	MRI lesion locations	SARS CoV-2
34583213	2021	*	population
33743552	2021	*	prognostic
33717149	2021	*	prognostic
34583946	2022	pediatric patients only	pediatric
		no information on types of attacks or	
34379008	2022	MRI lesion locations	MRI
36494385	2022	MOG-AD focused	MOG-AD
36370634	2022	*	clinical trial
35851754	2022	single centred	prognostic
35452969	2022	*	MRI
35078127	2022	pediatric patients only	pediatric
		no information on types of attacks or	
37769428	2023	MRI lesion locations	clinical trial
37393803	2023	pediatric patients only	pediatric
37268404	2023	*	prognostic
36907119	2023	*	prognostic

		no information on types of attacks or	
36786424	2023	MRI lesion locations	prognostic
		no information on types of attacks or	exploratory &
36693760	2023	MRI lesion locations	SARS-CoV-2
36521387	2023	MOG-AD focused	MOG-AD
36453614	2023	*	diagnostic

Abbreviations: MOG-AD = myelin oligodendrocyte glycoprotein associated disorder, SARS CoV-2 = Severe-acute-respiratory-syndrome-related coronavirus-2, CROCTINO = collaborative retrospective study on retinal optical coherence tomography in neuromyelitis optica, MS = multiple sclerosis.

* is used to denote studies used for further meta-analysis.

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Table S2 | Meta-analysis: Pooled Multi-centered NMOSD Studies (n = 32)

Characteristics Pooled	Mean	SD	IQR
Subjects (n)	145.4	104.8	120.3
Female (%)	82.6	11.2	7.2
AQP4-IgG Seropositive (%)	68.7	25.2	42.0
Optic Neuritis (%)	50.3	23.8	19.7
Myelitis (%)	50.3	22.9	23.8
Area postrema or Brainstem Syndrome (%)	18.3	23	12.8
Combination of Event Phenotypes (%)	22.6	21.2	20.1
Abnormal Cerebral MRI (%)	46.2	24.5	38.4
Abnormal Spinal MRI (%)	66.8	17.7	20.5

Abbreviations: AQP4-IgG = aquaporin-4-IgG, NMOSD = neuromyelitis optica spectrum disorder, SD = standard deviation, IQR = interquartile range.

SUPPLEMENTAL METHODS

F. Hoffmann-La Roche Ltd. provided financial support in the form of an independent grant to the coordination and analysis centers. At the time of the research and manuscript drafting, none of the authors were employees of Roche. The researchers retained complete control over the design, methodology, and conduct of the research as well as the data and information submitted for publication. The funding did not influence the results or conclusions of the study.

Data collection

Briefly, study preparation began in January 2016, which entailed the set-up of the XNAT project infrastructure (<https://gjcfxnat.utahdcc.org/app/template/Login.vm>), development of electronic case report forms using REDCap (<https://redcap.utahdcc.org/redcap/>), and providing user manuals for data collection and transfer. Both XNAT and REDCap databases are housed at the clinical data coordination center. PAMRINO was officially launched in August 2017 and members of the GJCF-ICC were invited to participate in this collaborative MRI and clinical data study. For the entire PAMRINO cohort, we included subjects with a) NMOSD (2006 and/or the 2015 International Panel criteria (36,37)); b) LETM; c) recurrent ON; and d) healthy controls. MRI raw data were transferred by participating centres through TeamBeam (<https://www.teambeam.de/en/>, Skelio GmbH, Hamburg, Germany), a web-based medical data exchange service compliant with the General Data Protection Regulation in the European Union. We endeavoured to collect as much real-world data as possible to obtain a comprehensive view on how patients with NMOSD are currently being evaluated in the international community. Data from participating centers were included in a community effort and curated by the research group at the main coordination and analysis center with an end date of data collection on December 31, 2019. We collected imaging data from 525 patients with AQP4-IgG+ NMOSD with longitudinal MRI (over 20,000 individual MRI scans) and clinical data for 1245 visits. Clinical data collection was identical to the previously published CROCTINO study on optical coherence tomography (OCT) in NMOSD (38), however, updated questions on the total number of myelitis attacks and the date of the most recent SC relapse were added (CROCTINO/PAMRINO REDCap Code Book). Visual outcomes were not required. Eight centers provided data from a total of 97 patients with

AQP4-IgG+ NMOSD that overlapped in CROCTINO and PAMRINO. IRB approval was collected by each participating center prior to data sharing. Data transfer agreements were approved by each participating center and signed to indicate specific use of demographic, clinical, and imaging data for research purposes in CROCTINO and PAMRINO.

The CROCTINO/PAMRINO REDCap Code Book contains the questions in the electronic capture record form collected for the PAMRINO project in REDCap for all patients. Extensive data curation was performed to rectify missing or incorrectly entered data deemed important in our analyses (i.e. patient serostatus, the Kurtze expanded disability status scale (EDSS) score (39), and clinical attack data).

CROCTINO/PAMRINO REDCap Code Book

#	Variable / Field Name	Field Label <i>Field Note</i>	Field Attributes (Field Type, Validation, Choices, Calculations, etc.)
Instrument: Personal Details(personal_details)			
1	[studyid]	CROCTINO/ PAMRINO Subject ID	text, Required Field Annotation: (The patient ID consists of the Center ID + consecutive numbers, e.g. BER-001)
2	[circlesid]	CIRCLES Subject ID <i>if applicable</i>	text
3	[cirrus_id]	CIRRUS ID <i>if applicable</i>	text
4	[topcon_id]	TOPCON ID <i>if applicable</i>	text
5	[sex]	Section Header: <i>Demographics</i> Sex	radio, Required 1 female 2 male 3 other
6	[year_of_birth]	Year of birth <i>e.g. 1987</i>	text (integer, Min: 1900, Max: 2015), Required
7	[month_of_birth]	Month of birth	dropdown (autocomplete, Min: 1, Max: 12), Required 1 January 2 February 3 March 4 April 5 May 6 June 7 July 8 August 9 September 10 October 11 November 12 December
8	[ethnicity]	Ethnicity/ Race <i>Select only one racial</i>	radio, Required 1 American Indian or Alaska Native

		<i>designation the participant MOST CLOSELY identifies with!</i>	2 Asian 3 Black or African American 4 Hispanic or Latino 5 Native Hawaiian or Other Pacific Islander 6 White 7 Other 8 Not reported
9	[ethnicity_other] Show the field ONLY if: [ethnicity] = '7'	Other ethnicity <i>If other: Please specify!</i>	text
10	[ethnicity_additional]	If the patient identifies with additional racial designations, select all that apply!	checkbox 1 ethnicity_additional__ _1 American Indian or Alaska Native 2 ethnicity_additional__ _2 Asian 3 ethnicity_additional__ _3 Black or African American 4 ethnicity_additional__ _4 Hispanic or Latino 5 ethnicity_additional__ _5 Native Hawaiian or Other Pacific Islander 6 ethnicity_additional__ _6 White 7 ethnicity_additional__ _7 Other 8 ethnicity_additional__ _8 Not reported
11	[ethnicity_additional_other] Show the field ONLY if: [ethnicity_additional(7)] = '1'	Other additional ethnicity <i>If other: Please specify!</i>	text

12	[handedness]	Handedness	radio 1 Right 2 Left 3 Unknown
13	[height]	Height <i>in cm</i>	text (integer, Min: 50, Max: 300)
14	[personal_details_complete]	Section Header: <i>Form Status Complete?</i>	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: General Details(general_details)			
15	[baseline_visit_date]	Section Header: <i>Please fill in the visit specific general details for the subject here. Visit Date</i>	text (date_dmy)
16	[weight]	Weight <i>in kg, e.g. 65.5</i>	text (number, Min: 20, Max: 300)
17	[ophthl_comorb]	Ophthalmolo -gic comorbidities <i>other than optic neuritis related</i>	radio, Required 1 Unknown 2 No (excluded by examination) 3 No (excluded by history taking) 4 Yes
18	[ophthl_comorb_specify] Show the field ONLY if: [ophthl_comorb] = '4'	Ophthalmolo -gic comorbidities - please specify <i>please indicate side (left/right)</i>	notes, Required
19	[other_comorb]	Other comorbidities	radio, Required 1 Unknown 2 No

			3 Yes
20	[other_comorb_specify] Show the field ONLY if: [other_comorb] = '3'	Other comorbidities - please specify	notes, Required
21	[general_details_complete]	Section Header: <i>Form Status Complete?</i>	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: General Details - Update at Follow up visit(general_details_update_at_follow_up_visit)			
22	[weight_fu]	Section Header: <i>Please fill in the visit specific general details for the subject here. Weight in kg, e.g. 65.5</i>	text (number, Min: 20, Max: 300)
23	[visit_date_fu]	Visit date	text (date_dmy)
24	[change_ophthal_comorb_fu]	Change in ophthalmolo- gic comorbidities ?	yesno, Required 1 Yes 0 No
25	[ophthl_comorb_specify_fu] Show the field ONLY if: [change_ophthal_comorb_fu] = '1'	Ophthalmolo- gic comorbidities - please specify <i>other than optic neuritis related</i>	notes, Required
26	[change_other_comorb]	Change in other comorbidities ?	yesno, Required 1 Yes 0 No
27	[other_comorb_specify_fu] Show the field ONLY if: [change_other_comorb] = '1'	Other comorbidities	notes, Required

		- please specify	
28	[general_details_update_at_follow_up_visit_complete]	Section Header: <i>Form Status</i> Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: Clinical Data (clinical_data)			
29	[clinical_info]	Enter the clinical information for this subject at time of Baseline visit here.	descriptive
30	[symptom_onset]	Section Header: <i>Diagnosis Symptom onset</i> <i>If the day of the first attack onset is unknown, please select the 1st day of the month!</i>	text (date_dmy), Required
31	[nmosd_diagnosis]	What is the patient's diagnosis? (multiple answers possible)	checkbox, Required 1 nmosd_diagnosis__1 NMO (2006 Wingerchuk criteria) 2 nmosd_diagnosis__2 AQP4-IgG seropositive NMOSD (2015 Wingerchuk criteria) 3 nmosd_diagnosis__3 AQP4-IgG seronegative NMOSD (2015 Wingerchuk criteria) 4 nmosd_diagnosis__4 MOG-IgG associated Encephalomyelitis/NMOSD

			<p>5 nmosd_di RON/CRION (Recurrent agnosis__ Optic Neuritis)_5</p> <p>6 nmosd_di LETM (Longitudinal agnosis__ Extensive Transverse_6 Myelitis)</p>
32	[aqp4_igg]	AQP4-IgG status at time of examination	<p>radio, Required</p> <p>1 Seropositive</p> <p>2 Currently seronegative, but at least one previous test was positive</p> <p>3 Seronegative</p> <p>4 Not known/Never assessed</p>
33	[mog_igg]	MOG-IgG status at time of examination	<p>radio, Required</p> <p>1 Seropositive</p> <p>2 Currently seronegative, but at least one previous test was positive</p> <p>3 Seronegative</p> <p>4 Not known/Never assessed</p>
34	[edss]	<p>Section Header:</p> <p><i>Expanded Disability Status Scale (EDSS)</i></p> <p>EDSS score at time of examination</p>	<p>dropdown (autocomplete)</p> <p>0 0</p> <p>1 1.0</p> <p>1.5 1.5</p> <p>2 2.0</p> <p>2.5 2.5</p> <p>3 3.0</p> <p>3.5 3.5</p> <p>4 4.0</p> <p>4.5 4.5</p> <p>5 5.0</p> <p>5.5 5.5</p> <p>6 6.0</p> <p>6.5 6.5</p> <p>7 7.0</p> <p>7.5 7.5</p> <p>8 8.0</p> <p>8.5 8.5</p> <p>9 9.0</p> <p>9.5 9.5</p>

35	[od_on]	Section Header: <i>Optic Neuritis</i> Has the patient experienced optic neuritis in the RIGHT eye	yesno, Required 1 Yes 0 No
36	[od_number_on] Show the field ONLY if: [od_on] = '1'	Right Eye: Total number of optic neuritis episodes	text (number, Min: 1, Max: 50), Required
37	[od_date_last_on] Show the field ONLY if: [od_on] = '1'	Right Eye: Date of last optic neuritis	text (date_dmy), Required
38	[os_on]	Has the patient experienced optic neuritis in the LEFT eye	yesno, Required 1 Yes 0 No
39	[os_number_on] Show the field ONLY if: [os_on] = '1'	Left Eye: Total number of optic neuritis episodes	text (number, Min: 1, Max: 50), Required
40	[os_date_last_on] Show the field ONLY if: [os_on] = '1'	Left Eye: Date of last optic neuritis	text (date_dmy), Required
41	[simultaneous_bilateral_on] Show the field ONLY if: [od_on] = '1' and [os_on] = '1'	Has the patient ever experienced simultaneous bilateral ON?	radio, Required 1 Yes 2 No 3 Unknown
42	[myelitis]	Section Header: <i>Has</i>	radio (Matrix), Required 1 Yes

		<i>the patient experienced other NMOSD defining attacks?</i> Transverse Myelitis	2 No 3 Unknown
43	[areapostrema]	Acute Area Postrema Syndrome	radio (Matrix), Required 1 Yes 2 No 3 Unknown Field Annotation: Episode of otherwise unexplained hiccups or nausea and vomiting
44	[brainstem]	Acute Brainstem Syndromes	radio (Matrix), Required 1 Yes 2 No 3 Unknown
45	[diencephalic]	Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions	radio (Matrix), Required 1 Yes 2 No 3 Unknown
46	[cerebral]	Symptomatic cerebral syndrome with NMOSD-typical brain lesions	radio (Matrix), Required 1 Yes 2 No 3 Unknown
47	[myel_number] Show the field ONLY if: [myelitis] = '1'	Total number of myelitis episodes (optional)	text

48	[myel_date] Show the field ONLY if: [myelitis] = '1'	Date of last myelitis (optional)	text (date_dmy)
49	[areapostrema_number] Show the field ONLY if: [areapostrema] = '1'	Total number of area postrema syndrome episodes (optional)	text
50	[areapostrema_date] Show the field ONLY if: [areapostrema] = '1'	Date of last area postrema syndrome episode (optional)	text (date_dmy)
51	[brainstem_number] Show the field ONLY if: [brainstem] = '1'	Total number of brainstem syndromes episodes (optional)	text
52	[brainstem_date] Show the field ONLY if: [brainstem] = '1'	Date of last brainstem syndromes episode (optional)	text (date_dmy)
53	[comments_nmosd_attacks]	Comments	notes
54	[last_attack]	Onset date of last disease attack or relapse before examination	text (date_dmy), Required
55	[alemtuzumab]	Section Header: OPTIONAL: Treatment Alemtuzu- mab	radio (Matrix) 1 Current 2 Previous use
56	[azathioprine]	Azathioprine	radio (Matrix) 1 Current 2 Previous use

57	[cyclophosphamide]	Cyclophosph- -amide	radio (Matrix) 1 Current 2 Previous use
58	[cyclosporine]	Cyclosporine	radio (Matrix) 1 Current 2 Previous use
59	[eculizumab]	Eculizumab	radio (Matrix) 1 Current 2 Previous use
60	[fingolimod]	Fingolimod	radio (Matrix) 1 Current 2 Previous use
61	[glatiramer_acetate]	Glatiramer acetate	radio (Matrix) 1 Current 2 Previous use
62	[interferon_beta_1a]	Interferon beta 1a	radio (Matrix) 1 Current 2 Previous use
63	[interferon_beta_1b]	Interferon beta 1b	radio (Matrix) 1 Current 2 Previous use
64	[ivig]	IVIG	radio (Matrix) 1 Current 2 Previous use
65	[methotrexate]	Methotre- xate	radio (Matrix) 1 Current 2 Previous use
66	[mitoxantrone]	Mitoxan- trone	radio (Matrix) 1 Current 2 Previous use
67	[mycophenolate_mofetil]	Mycophe- nolate mofetil	radio (Matrix) 1 Current 2 Previous use
68	[natalizumab]	Natalizumab	radio (Matrix) 1 Current 2 Previous use

69	[prednisone_oral]	Prednisone (oral)	radio (Matrix) 1 Current 2 Previous use
70	[rituximab]	Rituximab	radio (Matrix) 1 Current 2 Previous use
71	[tocilizumab]	Tocilizumab	radio (Matrix) 1 Current 2 Previous use
72	[tacrolimus]	Tacrolimus	radio (Matrix) 1 Current 2 Previous use
73	[other_therapy]	Other	radio (Matrix) 1 Current 2 Previous use
74	[other_treatment] Show the field ONLY if: [other_therapy] = '1' or [other_therapy] = '2'	If other therapy: please specify	notes
75	[clinical_data_complete]	Section Header: <i>Form Status</i> Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: Clinical Data - Update at Follow up visit visit(clinical_data_update_at_follow_up_visit)			
76	[nmosd_diagnosis_fu]	Section Header: <i>Enter changes in clinical information for this subject since last visit here.</i> What is the patient's diagnosis? (multiple answers possible)	checkbox, Required 1 nmosd_diagnosis_fu__1 NMO (2006 Wingerchuk criteria) 2 nmosd_diagnosis_fu__2 AQP4-IgG seropositive NMOSD (2015 Wingerchuk criteria) 3 nmosd_diagnosis_fu__3 AQP4-IgG seronegative NMOSD (2015 Wingerchuk criteria)

			<p>4 nmosd_diagnosis_fu__4 MOG-IgG associated Encephalomyelitis/NMOSD</p> <p>5 nmosd_diagnosis_fu__5 RON/CRION (Recurrent Optic Neuritis)</p> <p>6 nmosd_diagnosis_fu__6 LETM (Longitudinal Extensive Transverse Myelitis)</p>
77	[nmosd_diagnosis_other_fu] Show the field ONLY if: [nmosd_diagnosis(5)] = '1'	If other diagnosis: Please specify	notes
78	[aqp4_igg_fu]	AQP4-IgG status at time of examination	<p>radio, Required</p> <p>1 Seropositive</p> <p>2 Currently seronegative, but at least one previous test was positive</p> <p>3 Seronegative</p> <p>4 Not known/Never assessed</p>
79	[mog_igg_fu]	MOG-IgG status at time of examination	<p>radio, Required</p> <p>1 Seropositive</p> <p>2 Currently seronegative, but at least one previous test was positive</p> <p>3 Seronegative</p> <p>4 Not known/Never assessed</p>
80	[edss_fu]	Section Header: <i>Expanded Disability Status Scale (EDSS)</i> EDSS score at time of examination	<p>dropdown (autocomplete)</p> <p>0 0</p> <p>1 1.0</p> <p>1.5 1.5</p> <p>2 2.0</p> <p>2.5 2.5</p> <p>3 3.0</p> <p>3.5 3.5</p> <p>4 4.0</p> <p>4.5 4.5</p> <p>5 5.0</p> <p>5.5 5.5</p>

			6 6.0 6.5 6.5 7 7.0 7.5 7.5 8 8.0 8.5 8.5 9 9.0 9.5 9.5
81	[od_on_fu]	Section Header: <i>Optic Neuritis</i> Has the patient experienced a new episode of optic neuritis in the RIGHT eye? (Since last visit)	yesno, Required 1 Yes 0 No
82	[od_number_on_fu] Show the field ONLY if: [od_on_fu] = '1'	Right Eye: Number of NEW optic neuritis episodes since previous visit	text (number, Min: 1, Max: 50), Required
83	[od_time_date_last_on_fu] Show the field ONLY if: [od_on_fu] = '1'	Right Eye: Date of last optic neuritis	text (date_dmy), Required
84	[os_on_fu]	Has the patient experienced a new episode of optic neuritis in the LEFT eye (Since last visit)	yesno, Required 1 Yes 0 No

85	[os_number_on_fu] Show the field ONLY if: [os_on_fu] = '1'	Left Eye: Number of NEW optic neuritis episodes	text (number, Min: 1, Max: 50), Required
86	[os_data_last_on] Show the field ONLY if: [os_on_fu] = '1'	Left Eye: Date of last optic neuritis	text (date_dmy), Required
87	[myelitis_fu]	Section Header: <i>Has the patient experienced other NEW NMOSD defining attacks?</i> Transverse Myelitis	radio (Matrix), Required 1 Yes 2 No 3 Unknown
88	[areapostrema_fu]	Acute Area Postrema Syndrome	radio (Matrix), Required 1 Yes 2 No 3 Unknown Field Annotation: Episode of otherwise unexplained hiccups or nausea and vomiting
89	[brainstem_fu]	Acute Brainstem Syndromes	radio (Matrix), Required 1 Yes 2 No 3 Unknown
90	[diencephalic_fu]	Symptom- atic narcolepsy or acute diencephalic clinical syndrome with NMOSD- typical diencephalic MRI lesions	radio (Matrix), Required 1 Yes 2 No 3 Unknown

91	[cerebral_fu]	Symptomatic cerebral syndrome with NMOSD-typical brain lesions	radio (Matrix), Required 1 Yes 2 No 3 Unknown
92	[myelitis_fu_number] Show the field ONLY if: [myelitis_fu] = '1'	Number of NEW myelitis episodes since previous visit (optional)	text
93	[myelitis_fu_date] Show the field ONLY if: [myelitis_fu] = '1'	Date of last myelitis episode (optional)	text (date_dmy)
94	[areapostrema_fu_number] Show the field ONLY if: [areapostrema_fu] = '1'	Number of NEW area postrema syndrome episode (optional)	text
95	[areapostrema_fu_date] Show the field ONLY if: [areapostrema_fu] = '1'	Date of last area postrema episode (optional)	text (date_dmy)
96	[brainstem_fu_number] Show the field ONLY if: [brainstem_fu] = '1'	Number of NEW brainstem syndromes episode (optional)	text
97	[brainstem_fu_date] Show the field ONLY if: [brainstem_fu] = '1'	Date of last brainstem syndromes episode (optional)	text (date_dmy)
98	[comments_nmosd_attacks_fu]	Comments	notes
99	[last_attack_fu] Show the field ONLY if:	Onset date of last	text (date_dmy), Required

	[myelitis_fu] = '1' or [areapostrema_fu] = '1' or [brainstem_fu] = '1' or [diencephalic_fu] = '1' or [cerebral_fu] = '1'	disease attack or relapse before examination	
100	[alemtuzumab_fu]	Section Header: <i>OPTIONAL: Treatment Update Alemtuz- umab</i>	radio (Matrix) 1 Current 2 Previous use (Since last visit)
101	[azathioprine_fu]	Azathioprine	radio (Matrix) 1 Current 2 Previous use (Since last visit)
102	[cyclophosphamide_fu]	Cyclophosph- -amide	radio (Matrix) 1 Current 2 Previous use (Since last visit)
103	[cyclosporine_fu]	Cyclosporine	radio (Matrix) 1 Current 2 Previous use (Since last visit)
104	[eculizumab_fu]	Eculizumab	radio (Matrix) 1 Current 2 Previous use (Since last visit)
105	[fingolimod_fu]	Fingolimod	radio (Matrix) 1 Current 2 Previous use (Since last visit)
106	[glatiramer_acetate_fu]	Glatiramer acetate	radio (Matrix) 1 Current 2 Previous use (Since last visit)
107	[interferon_beta_1a_fu]	Interferon beta 1a	radio (Matrix) 1 Current 2 Previous use (Since last visit)
108	[interferon_beta_1b_fu]	Interferon beta 1b	radio (Matrix) 1 Current 2 Previous use (Since last visit)
109	[ivig_fu]	IVIG	radio (Matrix) 1 Current 2 Previous use (Since last visit)

110	[methotrexate_fu]	Methotrexate	radio (Matrix) 1 Current 2 Previous use (Since last visit)
111	[mitoxantrone_fu]	Mitoxantrone	radio (Matrix) 1 Current 2 Previous use (Since last visit)
112	[mycophenolate_mofetil_fu]	Mycophenolate mofetil	radio (Matrix) 1 Current 2 Previous use (Since last visit)
113	[natalizumab_fu]	Natalizumab	radio (Matrix) 1 Current 2 Previous use (Since last visit)
114	[prednisone_oral_fu]	Prednisone (oral)	radio (Matrix) 1 Current 2 Previous use (Since last visit)
115	[rituximab_fu]	Rituximab	radio (Matrix) 1 Current 2 Previous use (Since last visit)
116	[tocilizumab_fu]	Tocilizumab	radio (Matrix) 1 Current 2 Previous use (Since last visit)
117	[tacrolimus_fu]	Tacrolimus	radio (Matrix) 1 Current 2 Previous use (Since last visit)
118	[other_therapy_fu]	Other	radio (Matrix) 1 Current 2 Previous use (Since last visit)
119	[other_treatment_fu] Show the field ONLY if: [other_therapy_fu] = '1' or [other_therapy_fu] = '2'	If other therapy: please specify	notes
120	[clinical_data_update_at_follow_up_visit_complete]	Section Header: <i>Form Status</i> Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: Visual assessments (required for CROCTINO only)(visual_assessments)			
121	[hcva_correction]	Section Header: <i>Fill</i>	radio, Required

		<p><i>here the results of visual assessments at time of OCT (required only for CROCTINO)</i></p> <p>Visual acuity - Refractive error correction?</p>	<p>1 Not corrected (correction was not attempted or assessed)</p> <p>2 Habitually corrected (wearing usual eye-wear)</p> <p>3 Best corrected (refraction with corrective lenses by operator)</p>
122	[hcva_od]	Right Eye: Visual Acuity	<p>dropdown (autocomplete), Required</p> <p>m0.30 20/10, -0.30 logMAR, dec 2.0</p> <p>m0.20 20/12.5, -0.20 logMAR, dec 1.6</p> <p>m0.10 20/16, -0.10 logMAR, dec 1.25</p> <p>0.00 20/20, 0.00 logMAR, dec 1.0</p> <p>0.10 20/25, 0.10 logMAR, dec 0.8</p> <p>0.20 20/32, 0.20 logMAR, dec 0.63</p> <p>0.30 20/40, 0.30 logMAR, dec 0.5</p> <p>0.40 20/50, 0.40 logMAR, dec 0.4</p> <p>0.50 20/63, 0.50 logMAR, dec 0.32</p> <p>0.60 20/80, 0.60 logMAR, dec 0.25</p> <p>0.70 20/100, 0.70 logMAR, dec 0.2</p> <p>0.80 20/125, 0.80 logMAR, dec 0.16</p> <p>0.90 20/160, 0.90 logMAR, dec 0.125</p> <p>1.00 20/200, 1.00 logMAR, dec 0.1</p> <p>1.1 20/250, 1.1 logMAR, dec 0.08</p> <p>1.22 20/320, 1.22 logMAR, dec 0.063</p>

			<p>1.3 20/400, 1.3 logMAR, dec 0.05</p> <p>1.4 20/500, 1.4 logMAR, dec 0.04</p> <p>1.52 20/630, 1.52 logMAR, dec 0.03</p> <p>1.6 20/800, 1.6 logMAR, dec 0.025</p> <p>1.7 20/1000, 1.7 logMAR, 0.02</p> <p>1.8 20/1250, 1.8 logMAR, dec 0.016</p> <p>1.92 20/1600, 1.92 logMAR, dec 0.013</p> <p>2 counting fingers, 2.0 logMAR, dec 0.01</p> <p>3 hand motion (HM)</p> <p>4 light perception (LP)</p> <p>5 no light perception (NLP)</p>
123	[hcva_os]	Left Eye: Visual Acuity	<p>dropdown (autocomplete), Required</p> <p>m0.30 20/10, -0.30 logMAR, dec 2.0</p> <p>m0.20 20/12.5, -0.20 logMAR, dec 1.6</p> <p>m0.10 20/16, -0.10 logMAR, dec 1.25</p> <p>0.00 20/20, 0.00 logMAR, dec 1.0</p> <p>0.10 20/25, 0.10 logMAR, dec 0.8</p> <p>0.20 20/32, 0.20 logMAR, dec 0.63</p> <p>0.30 20/40, 0.30 logMAR, dec 0.5</p> <p>0.40 20/50, 0.40 logMAR, dec 0.4</p> <p>0.50 20/63, 0.50 logMAR, dec 0.32</p> <p>0.60 20/80, 0.60 logMAR, dec 0.25</p> <p>0.70 20/100, 0.70 logMAR, dec 0.2</p> <p>0.80 20/125, 0.80 logMAR, dec 0.16</p> <p>0.90 20/160, 0.90 logMAR, dec 0.125</p>

			<p>1.00 20/200, 1.00 logMAR, dec 0.1</p> <p>1.1 20/250, 1.1 logMAR, dec 0.08</p> <p>1.22 20/320, 1.22 logMAR, dec 0.063</p> <p>1.3 20/400, 1.3 logMAR, dec 0.05</p> <p>1.4 20/500, 1.4 logMAR, dec 0.04</p> <p>1.52 20/630, 1.52 logMAR, dec 0.03</p> <p>1.6 20/800, 1.6 logMAR, dec 0.025</p> <p>1.7 20/1000, 1.7 logMAR, 0.02</p> <p>1.8 20/1250, 1.8 logMAR, dec 0.016</p> <p>1.92 20/1600, 1.92 logMAR, dec 0.013</p> <p>2 counting fingers, 2.0 logMAR, dec 0.01</p> <p>3 hand motion (HM)</p> <p>4 light perception (LP)</p> <p>5 no light perception (NLP)</p>
124	[hcva_ou]	OPTIONAL: Binocular Visual Acuity	<p>dropdown (autocomplete)</p> <p>m0.30 20/10, -0.30 logMAR, dec 2.0</p> <p>m0.20 20/12.5, -0.20 logMAR, dec 1.6</p> <p>m0.10 20/16, -0.10 logMAR, dec 1.25</p> <p>0.00 20/20, 0.00 logMAR, dec 1.0</p> <p>0.10 20/25, 0.10 logMAR, dec 0.8</p> <p>0.20 20/32, 0.20 logMAR, dec 0.63</p> <p>0.30 20/40, 0.30 logMAR, dec 0.5</p> <p>0.40 20/50, 0.40 logMAR, dec 0.4</p> <p>0.50 20/63, 0.50 logMAR, dec 0.32</p> <p>0.60 20/80, 0.60 logMAR, dec 0.25</p>

			<p>0.70 20/100, 0.70 logMAR, dec 0.2</p> <p>0.80 20/125, 0.80 logMAR, dec 0.16</p> <p>0.90 20/160, 0.90 logMAR, dec 0.125</p> <p>1.00 20/200, 1.00 logMAR, dec 0.1</p> <p>1.1 20/250, 1.1 logMAR, dec 0.08</p> <p>1.22 20/320, 1.22 logMAR, dec 0.063</p> <p>1.3 20/400, 1.3 logMAR, dec 0.05</p> <p>1.4 20/500, 1.4 logMAR, dec 0.04</p> <p>1.52 20/630, 1.52 logMAR, dec 0.03</p> <p>1.6 20/800, 1.6 logMAR, dec 0.025</p> <p>1.7 20/1000, 1.7 logMAR, 0.02</p> <p>1.8 20/1250, 1.8 logMAR, dec 0.016</p> <p>1.92 20/1600, 1.92 logMAR, dec 0.013</p> <p>2 counting fingers (CF), 2.0 logMAR, dec 0.01</p> <p>3 hand motion (HM)</p> <p>4 light perception (LP)</p> <p>5 no light perception (NLP)</p>
125	[lcla_correction]	<p>Section Header:</p> <p><i>OPTIONAL:</i></p> <p><i>Low contrast letter acuity (LCLA) measured with 2.5% contrast SLOAN charts</i></p>	<p>radio</p> <p>1 Not corrected (correction was not attempted or assessed)</p> <p>2 Habitually corrected (wearing usual eye-wear)</p> <p>3 Best corrected (refraction with corrective lenses by operator)</p>

		LCLA - Refractive error correction?	
126	[lcla_distance]	At which distance was LCLA testing performed? <i>in meters, e.g. 4.0</i>	text (number)
127	[lcva_od]	Right Eye: 2.5% Contrast Sloan Low Contrast Visual Acuity	dropdown (autocomplete) m0.30 20/10, -0.30 logMAR, dec 2.0 m0.20 20/12.5, -0.20 logMAR, dec 1.6 m0.10 20/16, -0.10 logMAR, dec 1.25 0.00 20/20, 0.00 logMAR, dec 1.0 0.10 20/25, 0.10 logMAR, dec 0.8 0.20 20/32, 0.20 logMAR, dec 0.63 0.30 20/40, 0.30 logMAR, dec 0.5 0.40 20/50, 0.40 logMAR, dec 0.4 0.50 20/63, 0.50 logMAR, dec 0.32 0.60 20/80, 0.60 logMAR, dec 0.25 0.70 20/100, 0.70 logMAR, dec 0.2 0.80 20/125, 0.80 logMAR, dec 0.16 0.90 20/160, 0.90 logMAR, dec 0.125 1.00 20/200, 1.00 logMAR, dec 0.1 2.00 no letters
128	[lcla_od]	Right Eye: 2.5% charts letter acuity (LCLA) (Number of correctly	text (number, Min: 0, Max: 70)

		identified letters) <i>Enter number of letters ONLY if you used the 70 letters Sloan chart!</i>	
129	[lcva_os]	Left Eye: 2.5% Contrast Sloan Low Contrast Visual Acuity	dropdown (autocomplete) m0.30 20/10, -0.30 logMAR, dec 2.0 m0.20 20/12.5, -0.20 logMAR, dec 1.6 m0.10 20/16, -0.10 logMAR, dec 1.25 0.00 20/20, 0.00 logMAR, dec 1.0 0.10 20/25, 0.10 logMAR, dec 0.8 0.20 20/32, 0.20 logMAR, dec 0.63 0.30 20/40, 0.30 logMAR, dec 0.5 0.40 20/50, 0.40 logMAR, dec 0.4 0.50 20/63, 0.50 logMAR, dec 0.32 0.60 20/80, 0.60 logMAR, dec 0.25 0.70 20/100, 0.70 logMAR, dec 0.2 0.80 20/125, 0.80 logMAR, dec 0.16 0.90 20/160, 0.90 logMAR, dec 0.125 1.00 20/200, 1.00 logMAR, dec 0.1 2.00 no letters
130	[lcla_os]	Left Eye: 2.5% charts letter acuity (LCLA) (Number of correctly identified letters)	text (number, Min: 0, Max: 70)

		Enter number of letters <i>ONLY</i> if you used the 70 letters Sloan chart!	
131	[vep_p100_od]	Section Header: <i>OPTIONAL:</i> <i>Visual evoked potentials (VEP)</i> Right Eye: P100 latency	radio 1 normal 2 prolonged 3 not analyzable
132	[vep_p100_os]	Left Eye: P100 latency	radio 1 normal 2 prolonged 3 not analyzable
133	[vf_device]	Section Header: <i>OPTIONAL:</i> <i>Visual fields</i> Which visual field device was used?	dropdown (autocomplete) 1 Humphrey Field Analyzer (Carl Zeiss meditec) 2 Octopus (Haag-Streit) 3 Heidelberg Edge Perimeter (HEP) - Heidelberg 4 Engineering 5 other - please specify
134	[vf_device_other] Show the field <i>ONLY</i> if: [vf_device] = '5'	If other device: Please specify!	text
135	[vf_protocol]	Protocol (including field size, e.g. "30-2" for 30 degrees temporally/ nasally from the centre of fixation)	text

136	[od_md]	Right Eye - Mean Deficit (MD)	text (number, Min: -20, Max: 20)
137	[od_psd]	Right Eye - Pattern standard deviation (PSD)	text (number, Min: -20, Max: 20)
138	[os_md]	Left Eye - Mean Deficit (MD)	text (number, Min: -20, Max: 20)
139	[os_psd]	Left Eye - Pattern standard deviation (PSD)	text (number, Min: -20, Max: 20)
140	[visual_assessments_complete]	Section Header: <i>Form Status</i> Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: OCT Image Data(oct_image_data_upload)			
Instrument: OCT Quality Control(quality_control)			
Instrument: OCT Data(oct_data)			
Instrument: CROCTINO/PAMRINO Participation(croctinopamrino_participation)			
202	[participation_croctino]	CROCTINO?	yesno, Required 1 Yes 0 No Field Annotation: @DEFAULT="0"
203	[participation_pamrino]	PAMRINO?	yesno, Required 1 Yes 0 No Field Annotation: @DEFAULT="1"
204	[croctinopamrino_participation_complete]	Section Header: <i>Form Status</i> Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete

Abbreviations: NMO = neuromyelitis optica, AQP4-IgG = aquaporin-4 immunoglobulin G, MOG-IgG = myelin oligodendrocyte glycoprotein immunoglobulin G, RON/CRION = recurrent optic neuritis/chronic relapsing idiopathic optic neuritis, logMAR = Logarithm of the Minimum Angle of Resolution, dec = visual decimal score, hcva = high contrast visual acuity, os = oculus sinister, od = oculus dexter, ou = oculus uterque.

SUPPLEMENTAL METHODS CONTINUED

Meta-analysis

Studies were excluded (n=23) from mean pooling separately for each parameter depending on availability of information on types of clinical attacks and/or MRI lesion locations in the publication. Several studies were excluded based on myelin oligodendrocyte glycoprotein (n=7), MS (n=1), pregnancy symptom (n=3), and pediatric patient (n=4) focused studies. One study was a single-centered study, which was also excluded.

MRI lesion analyses

Initial MRI assessment of lesion locations and characteristics were evaluated in early 2019 through consensus between CC and JW (expert neuroradiologist). After data collection was finalized in December 2019, a meeting with experts from participating centers took place to expand MRI assessment criteria for more detailed anatomical location information. These extended criteria were applied by VCS to re-evaluate patient MRIs previously assessed and the pending patient MRIs. Therefore, the complete MRI assessment based on the extended criteria for all patients was performed by VCS, between April 2020 and February 2021.

Cross-sectional MRI data overview

MR examinations at 3 Tesla (3T) magnetic field strength were available in 282 patients. The majority of sites acquired 2D T2-weighted (T2W)/Fluid Attenuated Inversion Recovery (FLAIR) (n=256) and 3D T1W (n=166). Supplemental Table 3 provides the number of patients with available imaging data for each anatomical compartment. Within each compartment, contrast-enhanced T1W (CE) series were not available in all subjects: T1W CE series could be assessed in 245 of the 320 patients with MR scans covering the brain and cerebellum (76.6%). The majority of SC scans were acquired using two different sequences, often from brainstem until D2/D3 and then from C7 to the sacrum. Thus, we have defined the upper segment and lower segment accordingly, to homogenize data annotation and, hence, included cervical SC in the upper SC and the thoracic SC and conus medullaris in the lower SC. T1W CE series covering the brainstem were available in 249/321 (77.6%) patients, comprising the upper SC in 251/329 patients (76.3%) and the lower SC in 242/322 patients

(75.2%). CE series in orbital MRI were available for the optic nerves in 122/152 (80.3%) patients and for the optic chiasm in 129/153 (84.3%) patients.

Since blinded reading of all MRI visits was performed, no definite assumption can be made on findings being acute or stable. From an imaging point of view, however, findings suggestive of acute lesions (for both the brain and the SC) are the presence of T2W/FLAIR/STIR hyperintensity with subtle to mild mass effect (tumefaction) due to inflammatory-related edema. In some cases, T1W hyperintensity due to contrast agent uptake ensues simultaneously, confirming a disruption of the blood-brain barrier, which may occur during acute inflammation. For chronic (or stable) lesions, usually the T2W/FLAIR/STIR hyperintensity remains, however without corresponding tumefactive and, in some cases, with parenchymal loss resulting in atrophy.

Clinical Phenotyping

MRI data with CE-T1W within 30 days after clinical attack were considered "Acute CE MRIs". These data were radiologically assessed for the presence of CE lesions per compartment (Brain, ON, SC) after an optic neuritis, myelitis, or any type of clinical attack (including brainstem and/or area postrema or combination attacks).

A group effect sizes comparison was performed on the baseline cross-sectional data to show differences between patients from international centers (Supplemental Figure S1) by calculating mean differences in group metrics with 500 bootstrap resampling for effect size measurement in relation to the first alphabetically listed center (Bangkok – BAN).

Table S3 | Imaging protocol information extracted from DICOM tags according to CNS compartment

	n	% of total n
Total Patients with MRI available	349	100
Brain MRI	341	97.7
1.5T brain MRI	227	65.0
3T brain MRI	282	80.8
2D T1-weighted brain scan	173	49.6
3D T1-weighted brain scan	100	28.6
2D T2-weighted brain scan	322	92.3
3D T2-weighted brain scan	136	40.0
Orbital MRI	166	47.6
MRI for CVS detection (SWI, T2*)	86	24.6
Spinal cord MRI	316	90.5
1.5T spinal cord MRI	202	57.9
3T spinal cord MRI	169	48.4
T1-weighted spinal cord MRI	263	75.4
T2-weighted spinal cord MRI	231	66.2
2D spinal cord MRI	311	89.1
3D spinal cord MRI	39	11.2

Note: not all DICOM tags contained accurate or complete information, most often due to the anonymization process (export for data sharing) from different radiology departments. For example, 341 “Brain MRI” labels were found in the raw DICOM headers, however only 320 Brain MRIs could be analyzed. Thus, no confidence intervals were calculated for this table. Abbreviations: 2D = 2-dimensional, 3D = 3-dimensional, CVS = central vein sign, SWI = susceptibility weighted imaging.

Table S4 | Available/usable MRI for cross-sectional analysis according to the anatomical compartments

Anatomical compartment		n=349 (100%)	95% CI (%)
Brain MRI	Brain and cerebellum	320 (91.7%)	89, 95
	Brainstem	321 (92%)	89, 95
Orbital MRI	Optic Nerves	152 (43.7%)	38, 49
	Chiasm	153 (44%)	39, 49
Spinal cord MRI	Upper spinal cord	322 (92.3%)	90, 95
	Lower Spinal cord	301 (86.3%)	83, 90

Abbreviations: CI = confidence interval.

Table S5 | Imaging sequence median slice thickness and slice gaps

MRI Coverage	Slice Thickness (mm)	Slice Gap (mm)
T1-Brain MRI	3.5 (0.8 – 9)	4.8 (0.5 – 10.5)
Median (Range)		
T2-Brain MRI	3 (0.7 – 9)	4 (0.5 – 12.4)
Median (Range)		
Spinal Cord	3 (0.9 – 5)	3.3 (0.3 – 5)
Median (Range)		

Table S6 | Patients (n) with available simultaneous multicompartmental scans

CNS Compartments Imaged Together	n/349 (%)	95% CI (%)
Brain + ON	149 (42.7)	38, 48
Brain + upper SC	247 (70.7)	66, 75
Brain + lower SC	213 (61.0)	56, 66
Brain + upper SC + lower SC	212 (60.7)	56, 66
ON + upper SC	109 (31.2)	26, 36
ON + lower SC	92 (26.4)	22, 31
ON + upper SC + lower SC	92 (26.4)	22, 31
Brain + ON + upper SC	107 (30.7)	26, 36
Brain + ON + lower SC	90 (25.8)	21, 30
Brain + ON + upper SC + lower SC	90 (25.8)	21, 30

Abbreviations: CNS = central nervous system, ON = optic nerves, SC = spinal cord.

Table S7 | Simultaneous lesion occurrence in all patients (n) with available scans

Combined Lesional Compartments	n/total (%)	95% CI
Brain + Chiasm	44/149 (29.5)	22, 37
Brain + ON	73/149 (49)	41, 57
Brain + upper SC	135/247 (54.7)	48, 61
Brain + lower SC	126/213 (59.2)	53, 66
Chiasm + upper SC	27/109 (24.8)	17, 33
Chiasm + lower SC	25/92 (27.2)	18, 36
ON + upper SC	43/109 (39.4)	30, 49
ON + lower SC	35/92 (38)	28, 48
Brain + Chiasm + upper SC	25/107 (23.4)	15, 31
Brain + Chiasm + lower SC	23/90 (25.6)	17, 35
Brain + ON + upper SC	37/107 (34.6)	26, 44
Brain + ON + lower SC	30/90 (33.3)	24, 43
Chiasm + ON + upper SC	25/109 (22.9)	15, 31
Chiasm + ON + lower SC	23/92 (25)	16, 34
Brain + Chiasm + ON + upper SC	22/107 (20.6)	13, 28
Brain + Chiasm + ON + lower SC	18/90 (20)	12, 28
Brain + Chiasm + ON + upper SC + lower SC	13/90 (14.4)	7, 22

Abbreviations: CI = confidence interval, ON = optic nerves, SC = spinal cord.

Table S8 | Patients (n) with available follow-up/longitudinal scans and median time/range in days

CNS compartment	n/total (%)	Median time [IQR] (days)
Brain	146/220 (66.4)	377 [462.75]
Brainstem	151/220 (68.6)	370 [467]
ON	58/220 (26.4)	369 [434.75]
Chiasm	59/220 (26.8)	376.5 [437]
Upper SC	159/220 (72.3)	358 [471.5]
Lower SC	137/220 (62.3)	356.5 [470.25]

Abbreviations: ON = optic nerves, SC = spinal cord, IQR = interquartile range.

Table S9 | Patients (n) with available acute scans (not necessarily CE) and median time/range in days from any last attack type

CNS compartment	n/total (%)	Median time [IQR] (days)
Brain	52/63 (82.5)	8 [12.75]
Brainstem	52/63 (82.5)	8 [14.25]
ON	37/63 (58.7)	7.5 [15.75]
Chiasm	36/63 (57.1)	9 [15.00]
Upper SC	58/63 (92.1)	9 [17]
Lower SC	50/63 (79.4)	8 [16]

Abbreviations: CE = contrast enhancing, CNS = central nervous system, ON = optic nerves, SC = spinal cord, IQR = interquartile range.

Table S10 | Longitudinal brain and spinal cord MRI lesion distribution in all patients (n) with available scans (total)

Lesion Location	n/total (%)	95% CI
New/increased count brain lesions		
multifocal	69/146 (47.3)	39, 55
subcortical	58/146 (39.7)	32, 48
lateral periventricular	41/146 (28.1)	21, 35
corpus callosum	18/146 (12.3)	7, 18
New ON lesions	10/58 (16.9)	-2, 5
posterior third	7/10 (70)	42, 98
central third	4/10 (40)	10, 70
anterior third	4/10 (40)	10, 70
New chiasm lesions	12/59 (20.3)	10, 31
New Upper SC lesions	19/159 (11.9)	7, 17
New Lower SC lesions	12/137 (8.8)	4, 14

Abbreviations: CI = confidence interval, ON = optic nerves, SC = spinal cord.

SUPPLEMENTAL RESULTS

Longitudinal MRI Data

Brain

Of the 63 patients who had radiologically indicative acute MRIs, 52 had brain MRI acquired within 30 days of any type of clinical relapse (Supplemental Table S9). Brain lesions were present in 44/52 (84.6%) patients, with 14/44 (31.8%) showing CE suggestive of acute lesions. Brain tumefactive lesions (40) were identified in only 8/52 (15.3%) patients, corresponding to myelitis attacks in 6/8 (75%) patients and optic neuritis attacks in the remaining 25% of patients.

Brain and SC MRI from 52/63 patients acquired within 30 days of any type of clinical relapse allowed for brainstem analysis (Supplemental Table S9). Among the 52 patients, 33 (63.5%) had brainstem lesions (18/33 in the medulla, 16/33 in the area postrema, and 8/33 in the pons). Eleven of 33 (33.3%) patients had CEL. New brainstem lesions were observed in 17/151 (11.2%) patients between 58 days and four years of follow-up, without lesions in the previous scan. Complete brainstem lesion resolution was observed in 9/151 (6.0%) patients between 45 days and five years of follow-up.

Optic Nerves

Longitudinal assessment revealed lesions on follow-up MRI in 36 patients: 26/36 (73%) had chronic ON lesions with some degree of atrophy; new T2W lesions were found in 10 patients, with CEs in 8/10 (80.0%); and all patients underwent MRI within 3 months of their last ON. None of the 36 patients showed a normal ON baseline MRI or lesion resolution over time. Most new lesions occurred in the posterior segment, followed by the central and anterior segments (Supplementary Table S10). Of the 63 patients with acute MRIs taken 30 days after any type of attack, 37 had MRIs in which ON lesions could be evaluated (Supplemental Table 9). Among the 37 patients, 20 (54.1%) had ON lesions, and 19/20 (95.0%) presented with CE.

Optic Chiasm

Among the 36 patients with orbital or cerebral scans indicative of radiologically acute findings (Supplemental Table 9), 8 (22.2%) had lesions in the chiasm, and 4/8 (50.0%) had CE. For all patients, a prior ON lesion was confirmed. None of the T2W-hyperintense chiasmatic lesions identified in the cohort resolved completely over time.

Spinal Cord

New upper SC lesions were identified in 19/159 (11.9%) patients without previous lesions, with a range of follow-up times between 71 days and 3.5 years. Complete resolution of upper SC lesions was observed in 13/159 (8.2%) patients between 48 days and 3 years of follow-up. New lower SC lesions developed in 12/137 (8.8%) patients who presented a normal SC baseline scan within 4 days to 4 years of follow-up (Supplemental Figure S1B). In 5/137 patients (3.7%), complete lesion resolution occurred between 37 days and 3 years.

Of the 63 patients with available acute MRIs, 58 had upper SC MRI (Supplemental Table 9), with 47 (81%) showing lesions and the majority exhibiting CE (n=37/47, 78.7%).

Of the 63 patients with available acute MRIs, 50 had lower SC MRI (Supplemental Table 9). Forty-three of these patients had lesions (86.0%), and 34/43 (79.1%) had CE. For all patients, a myelitis attack within the new lesion was confirmed.

MRI analysis of acute inflammation and summary of findings

ON CELs (14/19 – 74%) were often seen in acute CE MRIs within 15 days after any type of relapse, with a high incidence after optic neuritis.

Two SC CE lesions were found to be silent; however, for both lesions, affected patients had confirmed acute relapse - one with a severe optic neuritis with visual loss and the second patient with a severe brainstem attack following with visual loss due to optic neuritis several days after the clinical visit. No other silent lesions were found in the entire cohort.

Based on our findings from the meta-analysis, radiological readings (acute and longitudinal), and other single-center studies, we propose recommendations for MRI sequences that can serve as a starting point for standardized imaging protocols at radiology departments and/or at specialized NMOSD centers (Supplemental Table S11).

Supplemental References

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Table S11 | 1.5 or 3T MRI protocol recommendations for patients with AQP4-IgG+NMOSD monitoring and research

Location and Sequence	Analysis Recommendations
Brain: 3D isotropic sagittal T2-weighted or FLAIR* sequence, including coverage of the upper cervical cord	Clinical radiology: <ul style="list-style-type: none"> - Accurate lesion detection (dissemination in time and space), especially around the periventricular and juxtacortical regions - Simultaneous identification of brainstem/medullary lesions possible Experimental analysis: <ul style="list-style-type: none"> - Lesion load calculation (volumetric analysis)
Brain: 3D isotropic sagittal T1-weighted sequence, including coverage of the upper cervical cord with and without Gadolinium contrast agent	Clinical radiology: <ul style="list-style-type: none"> - Detection of contrast-enhancing T1W lesions in acute attack settings (within a week of any attack type) Experimental analysis: <ul style="list-style-type: none"> - Volumetric analysis of brain regions - Simultaneous volumetric analysis of upper cervical cord possible
Spinal cord: 2D sagittal T2- or PD-weighted or STIR sequence, covering both upper and lower cord regions; slice thickness $\leq 3\text{mm}$; followed by 2D axial T2- or PD-weighted sequence covering lesions detected in sagittal plane	Clinical radiology: <ul style="list-style-type: none"> - Accurate detection of lesions in the cord and location, dissemination in time and space - Spinal cord atrophy assessment
Spinal cord: 2D sagittal T1-weighted sequence, post i.v. gadolinium	Clinical radiology:

administration, covering both upper and lower cord regions; slice thickness \leq 3mm	<ul style="list-style-type: none">- Detection of contrast-enhancing lesions, thus, only required in acute attack settings (< 20 days from a myelitis attack)- Spinal cord atrophy assessment
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Orbits:	Clinical radiology:
Coronal 2D T2-weighted fat saturated	<ul style="list-style-type: none">- Detection of T2W hyperintense lesions in the ON and chiasm (dissemination in space and time)

Orbits:	Clinical radiology:
Coronal 2D T1-weighted fat saturated, post i.v. gadolinium administration	<ul style="list-style-type: none">- Detection of contrast-enhancing lesions, thus, only required in acute attack settings (< 15 days from an optic neuritis attack)

*The authors suggest FLAIR instead of traditional T2-weighted sequences for improved brain lesion detection.

Abbreviations: ON = optic nerve, 2D = 2-dimensional, 3D = 3-dimensional, i.v. = intravenous.

SUPPLEMENTAL DISCUSSION SECTION

Additionally, spinal imaging was available for all 5 patients, 4/5 of whom had cord lesions. LETM was found in 3 patients, suggesting a preferential NMOSD diagnosis for these patients, whereas short segment TM affecting both the upper SC and lower SC was observed in 1/4 patients. However, few phenotypes expressing both MS and NMOSD imaging characteristics may exist.

SUPPLEMENTAL LIMITATIONS SECTION

Due to the large-scale real-world data collection, without restrictions based on MRI sequences or matching clinical visits, we could not assess attack-related treatments or monitor chronic lesions using contrast agents. Also because of the low number of acute MRIs and follow-up, determination of CE in different CNS compartments could not be statistically assessed. However, SC CELs seem to persist the longest, particularly after a myelitis attack. Our acute longitudinal subcohort indicates blood–brain barrier leakage within 2 weeks of optic neuritis or disease-related relapse in the brain, ON, and chiasm, in contrast to the SC. Larger, prospective studies are required to evaluate whether CELs are observed only in attack-related region(s) and persist after relapse.

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