Clinical features of neuromyelitis optica in children

US Network of Pediatric MS Centers report

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Tanuja Chitnis, MD
Jayne Ness, MD, PhD
Lauren Krupp, MD
Emmanuelle Waubant, MD, PhD
Tyler Hunt, MStat
Cody S. Olsen, MS
Moses Rodriguez, MD
Tim Lotze, MD
Mark Gorman, MD
Leslie Benson, MD
Anita Belman, MD
Bianca Weinstock-Guttman, MD
Greg Aaen, MD
Jennifer Graves, MD, PhD
Marc Patterson, MD
John W. Rose, MD
T. Charles Casper, PhD

Correspondence to Dr. Chitnis: tchitnis@rics.bwh.harvard.edu

ABSTRACT

Objective: To compare clinical features of pediatric neuromyelitis optica (NMO) to other pediatric demyelinating diseases.

Methods: Review of a prospective multicenter database on children with demyelinating diseases. Case summaries documenting clinical and laboratory features were reviewed by an adjudication panel. Diagnoses were assigned in the following categories: multiple sclerosis (MS), acute disseminated encephalomyelitis, NMO, and recurrent demyelinating disease not otherwise specified.

Results: Thirty-eight cases of NMO were identified by review panel, 97% of which met the revised International Panel on NMO Diagnosis NMO-SD 2014 criteria, but only 49% met 2006 Wingerchuk criteria. Serum or CSF NMO immunoglobulin G (IgG) was positive in 65% of NMO cases that were tested; however, some patients became seropositive more than 3 years after onset despite serial testing. No patient had positive CSF NMO IgG and negative serum NMO IgG in contemporaneous samples. Other than race ($p = 0.02$) and borderline findings for sex ($p = 0.07$), NMO IgG seropositive patients did not differ in demographic, clinical, or laboratory features from seronegatives. Visual, motor, and constitutional symptoms (including vomiting, fever, and seizures) were the most common presenting features of NMO. Initiation of disease-modifying treatment was delayed in NMO vs MS. Two years after onset, patients with NMO had higher attack rates, greater disability accrual measured by overall Expanded Disability Status Scale score, and visual scores than did patients with MS.

Conclusion: The new criteria for NMO spectrum disorders apply well to the pediatric setting, and given significant delay in treatment of NMO compared to pediatric MS and worse short-term outcomes, it is imperative to apply these to improve access to treatment. *Neurology*® 2016;86:245–252

GLOSSARY

ADEM = acute disseminated encephalomyelitis; **DD-NOS** = recurrent demyelinating disease not otherwise specified; **EDSS** = Expanded Disability Status Scale; **IgG** = immunoglobulin G; **IPMSSG** = International Pediatric Multiple Sclerosis Study Group; **IPND** = International Panel for NMO Diagnosis; **IQR** = interquartile range; **IT** = infratentorial; **LETM** = longitudinally extensive transverse myelitis; **MOG** = myelin oligodendrocyte glycoprotein; **MS** = multiple sclerosis; **NMO** = neuromyelitis optica; **ON** = optic neuritis; **PLEX** = plasma exchange.

Approximately 4% of neuromyelitis optica (NMO) cases are reported to be pediatric onset.[1,2] Early differentiation of NMO from other childhood demyelinating disorders including acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS) is critical for instituting appropriate therapy. Reports on pediatric NMO are often limited to small series or case reports,[2–6] most of which have focused on NMO immunoglobulin G (IgG)–seropositive patients. The largest series from the Mayo Clinic described a cohort of 88 children seropositive for NMO

Supplemental data at Neurology.org

From Partners Multiple Sclerosis Center (T.C.), Department of Neurology, Brigham and Women's Hospital, Brookline; Partners Pediatric Multiple Sclerosis Center (T.C.), Massachusetts General Hospital for Children, Boston; University of Alabama Center for Pediatric Onset Demyelinating Disease (J.N.), Children's Hospital of Alabama, Birmingham; the Lourie Center for Pediatric MS, Stony Brook Children's Hospital (L.K., A.B.), New York, NY; the Department of Neurology (E.W., J.G.) and the Department of Pediatrics, Benioff Children's Hospital (E.W.), University of California, San Francisco; the Departments of Pediatrics (T.H., C.S.O., T.C.C.) and Neurology (J.W.R.), University of Utah, Salt Lake City; Mayo Clinic's Pediatric MS Center (M.R., M.P.), Rochester, MN; Blue Bird Circle Multiple Sclerosis Center (T.L.), Baylor College of Medicine, Houston, TX; Boston Children's Hospital (M.G., L.B.), MA; the Pediatric Multiple Sclerosis Center (B.W.-G.), Jacobs Neurological Institute, SUNY Buffalo, New York, NY; and Pediatric MS Center at Loma Linda University Children's Hospital (G.A.), CA.

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IgG antibody.[2] Another series of 9 children with demyelinating disease included a description of children with relapsing NMO phenotype, 7 of whom were seropositive for NMO IgG antibody.[5]

The goal of this study was to characterize the demographic and clinical features in pediatric patients with NMO spectrum disorders relative to MS and ADEM and to test diagnostic criteria for NMO,[7–11] including the recently proposed International Panel for NMO Diagnosis (IPND 2015) criteria.[9]

METHODS

Study setting. The US Network of Pediatric MS Centers is a group of 9 centers funded by the National MS Society that serve as regional referral centers for children and adolescents with demyelinating diseases of the CNS. These sites include Boston Children's Hospital, Loma Linda Children's Hospital, Massachusetts General Hospital, Mayo Clinic, SUNY-StonyBrook, SUNY-Buffalo, Texas Children's Hospital, University of Alabama, and University of California San Francisco. Clinical data have been prospectively collected from pediatric patients with acquired CNS demyelinating diseases since May 2011, using standardized case report forms, including demographic features, neurologic examinations at visits, attack characteristics, and treatment information.[12] Data are entered into an OpenClinica database, housed at the University of Utah Data Coordinating and Analysis Center.

Patients. Four groups of patients were identified from the US Network of Pediatric MS Centers database seen between May 1, 2011, and December 31, 2013: those with a treating physician diagnosis of (1) NMO, (2) MS, (3) ADEM, or (4) any recurrent forms of CNS demyelinating disease not falling into the prior categories (recurrent demyelinating disease not otherwise specified [DD-NOS]).

Summary case report forms were generated including age at onset, diagnoses at visits, relapse features, results of NMO IgG testing in serum and CSF, presence of CSF oligoclonal bands, and treatment history. Qualitative MRI review was performed by site investigators on NMO cases including the presence of a longitudinally extensive transverse myelitis (LETM) and the fulfillment of Paty or Barkhof brain MRI criteria.[13] Each case was reviewed by at least 2/4 members of a clinical review panel (T.C., J.N., L.K., E.W.) and assigned the following diagnostic categories:

1. NMO meeting 2006 Wingerchuk[8] criteria or consensus by the clinical review panel (n = 38).
2. Pediatric MS meeting International Pediatric Multiple Sclerosis Study Group (IPMSSG) 2013 consensus criteria[14] (n = 150).
3. ADEM meeting IPMSSG consensus criteria[14] and with at least 2 years of follow-up with no further attacks (n = 24).
4. Recurrent DD-NOS: demyelinating disorders with >1 attack, not meeting definitions 1–3 (n = 26).

We assessed whether NMO cases met the updated IPND 2015 diagnostic criteria for NMO,[9] which divide patients into NMO-IgG seropositive and NMO-IgG seronegative. Seropositive patients are required to have at least one of the following core clinical characteristics: optic neuritis (ON), transverse myelitis, area postrema syndrome, acute brainstem syndrome, narcolepsy or diencephalic syndrome, or cerebral syndrome with NMO spectrum disorder–typical brain lesions. Only the first 4 of these criteria could be assessed in our cohort, as the last 2 are not collected as part of the standard dataset. Seronegative patients are required to have at least 2 core clinical characteristics of the following: (1a) at least 1 core clinical characteristic must be ON, acute myelitis with LETM, or area postrema syndrome; (1b) dissemination in space; (1c) fulfillment of additional MRI requirements, as applicable; (2) negative test for aquaporin-4 IgG using best available assay, or testing unavailable; (3) no better explanation for the clinical syndrome.

Statistical analysis. We described study populations using counts and relative frequencies for categorical variables, and means and standard deviations, or medians and interquartile ranges (IQR, or 75th percentile–25th percentile), for continuous variables. We reported the number of patients with available data for each description due to varying rates of unknown data. Descriptions included demographics, laboratory results, first attack locations and symptoms, and disease course. History of other autoimmune diseases of the patient and first-degree relatives (i.e., mother, father, full sibling), treatments, and timing of those treatments are also described.

We tested for associations between diagnosis classifications using Fisher exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Differences between patients with seronegative and seropositive NMO were tested using the same methods. Differences were considered significant when $p < 0.05$. Analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Standard protocol approvals, registrations, and patient consents. Ethics committees of participating institutions approved this study. The University of Utah Data Coordinating and Analysis Center maintains the human subject research protocol for the centralized collection and storage of data from all participating sites.

RESULTS

Patient groups. We identified 38 patients with pediatric NMO, 150 MS, 24 ADEM, and 26 recurrent DD-NOS, according to our reviewer classification criteria (table 1).

Fulfillment of diagnostic criteria for NMO. We tested recent NMO criteria in 37/38 patients. One patient did not have sufficient information. Only 49% (18/37) of the reviewer-classified patients with NMO met the 2006 Wingerchuk diagnostic criteria for NMO.[8] Thirteen patients were NMO IgG seropositive, yet had only one of the 2 core symptoms of ON or transverse myelitis. A total of 28/37 patients with NMO had LETM on their first available MRI scans. Of the reviewer-classified patients with NMO, approximately 1/3 (12/37) met Paty MRI criteria, including 9 who also met Barkhof MRI criteria: 7/37 (Paty) and 3/37 (Barkhof) on their first available scan.

Updated diagnostic criteria for NMO have been proposed recently. Using this subset of criteria features as described in the methods, 36/37 (97%) reviewer-defined patients with NMO fit the updated diagnostic criteria.[9]

Demographic characteristics. The youngest patient within the pediatric NMO group was 16 months at

Table 1 Demographics of patients with neuromyelitis optica (NMO), multiple sclerosis (MS), or acute disseminated encephalomyelitis (ADEM)[a]

	NMO (n = 38)	MS (n = 150)	ADEM (n = 24)
Age onset, y			
Mean (SD)[b,c]	10.2 (4.7)	13.5 (3.8)	4.8 (2.9)
Age <11 y[b,c]	20 (54)	30 (20)	23 (96)
Sex			
Male	12 (32)	56 (37)	14 (58)
Female	26 (68)	94 (63)	10 (42)
Race[b,c]			
White	14 (37)	91 (61)	19 (79)
Black/African American	14 (37)	20 (13)	1 (4)
Multiracial	2 (5)	8 (5)	0 (0)
Asian/East Asian	0 (0)	4 (3)	1 (4)
Asian/South Asian	3 (8)	0 (0)	0 (0)
Asian/Southeast Asian	1 (3)	2 (1)	0 (0)
American Indian/Alaskan native	0 (0)	2 (1)	0 (0)
Native Hawaiian or Pacific Islander	0 (0)	1 (1)	0 (0)
Unknown	4 (11)	22 (15)	3 (13)
Ethnicity[b]			
Non-Hispanic/non-Latino	29 (76)	91 (61)	17 (71)
Hispanic/Latino	5 (13)	46 (31)	5 (21)
Unknown	4 (11)	13 (9)	2 (8)

[a] Frequency (%) given, unless otherwise specified. Age at onset missing for 1 patient with NMO.
[b] p Value <0.05 comparing NMO vs MS according to a Wilcoxon rank-sum test for age or Fisher exact test for all others; test for race compares white vs all others excluding unknown; test for ethnicity compares Hispanic/Latino vs non-Hispanic/non-Latino.
[c] p Value <0.05 comparing NMO vs ADEM according to the tests described above.

onset. Mean age at onset (years) was 10.2 ± 4.7 in NMO, 13.5 ± 3.8 in MS, and 4.8 ± 2.9 in ADEM (table 1). Onset prior to age 11 years was more common in ADEM (96%) and less common in MS (20%) and NMO (54%, $p < 0.0001$ both comparisons). Figure 1 presents the distribution of age at onset for all diagnosis classifications.

The percentage of male participants was similar in the NMO (32%) and MS (37%) groups. In contrast, the ADEM cases were more frequently male (58%) compared to NMO cases ($p = 0.06$). The ratio of female to male in patients with NMO <11 years was 1.5:1, and in those ≥11 years, 3.25:1 (figure 2). In contrast, the female:male ratio in MS <11 was 1.1:1, and in MS ≥11 was 1.86:1; in ADEM, the ratio was 0.77:1 (in <11) and the ≥11 group was exclusively male.

Nonwhite race was reported more frequently in NMO vs MS or ADEM ($p < 0.01$, both comparisons). Table 1 shows patient's reported race and ethnicity by group. Among patients with NMO, 37% were African American, while 11% were Asian. Hispanic/Latino ethnicity was reported in 13% NMO, 31% MS, and 21% ADEM cases.

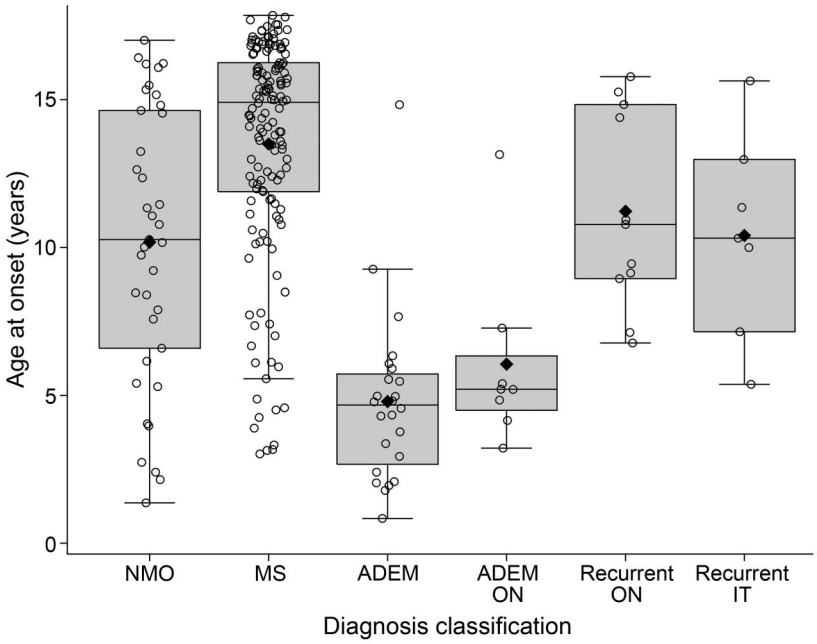
History of other autoimmune disease. Frequency of other autoimmune diseases occurring in the patients as well as first-degree relatives is reported in figures e-1 and e-2 on the *Neurology*® Web site at Neurology.org. Patients with NMO (16%) and MS (9%) had similar rates of additional autoimmune disorders. Of patients with NMO, 42% had first-degree relatives with an autoimmune disease compared with 32% of patients with MS.

NMO-IgG results. A total of 37/38 patients with NMO had serum or CSF tested for NMO-IgG. NMO-IgG was present in 65% (24/37) of NMO cases: 60% (21/35) in serum and 50% (7/14) in CSF. No patient had positive CSF NMO-IgG and negative serum NMO-IgG in contemporaneous samples. Two patients had positive CSF NMO-IgG without contemporaneous serum testing performed. One of these patients had positive CSF 2 years after negative serum samples; however, a concomitant serum sample was not drawn at the time of CSF analysis. Of the 24 seropositive patients with NMO, 19 (79%) were positive the first time they were tested (mean time after disease onset 11.3 months; SD 15.0; range: 0–48 months), 4 became positive the 2nd time (mean time after disease onset 26.5 months; SD 17.4; range 3–45 months), and 1 the 3rd time (39.0 months from onset). Of 23 seropositive patients with information about the timing of the test, 57% tested positive within 12 months of disease onset, 13% within 12–23 months, 13% within 24–35 months, and 17% at 36 months or more. NMO-IgG was absent in patients with MS (44% tested, 0/66), patients with ADEM (42% tested, 0/10) and patients with recurrent DD-NOS (81% tested, 0/21).

CSF results. Results of first CSF analysis are presented in table 2 (NMO, MS, and ADEM) and table e-1 (recurrent DD-NOS). Mean CSF leukocyte count was higher in NMO vs MS ($p = 0.01$), but not different vs ADEM ($p = 0.88$). Percent CSF neutrophils were highest in ADEM, but not different from the other groups (NMO 6.9 ± 12.5, MS 8.1 ± 11.5, $p = 0.53$; ADEM 21.2 ± 22.9, $p = 0.06$). When all documented CSF laboratory results were included in the analysis, CSF oligoclonal bands were differentially present in NMO (31%), MS (68%), and ADEM (0%) ($p < 0.01$ comparing NMO and MS; $p = 0.08$ comparing NMO and ADEM). Similarly, IgG index was elevated in 30% of NMO cases, 63% of MS cases ($p = 0.01$ vs NMO), and 22% of ADEM cases ($p = 1.0$ vs NMO).

First attack features. We compared first symptoms as well as first attack locations in the different groups (table 3). Visual, motor, and constitutional symptoms

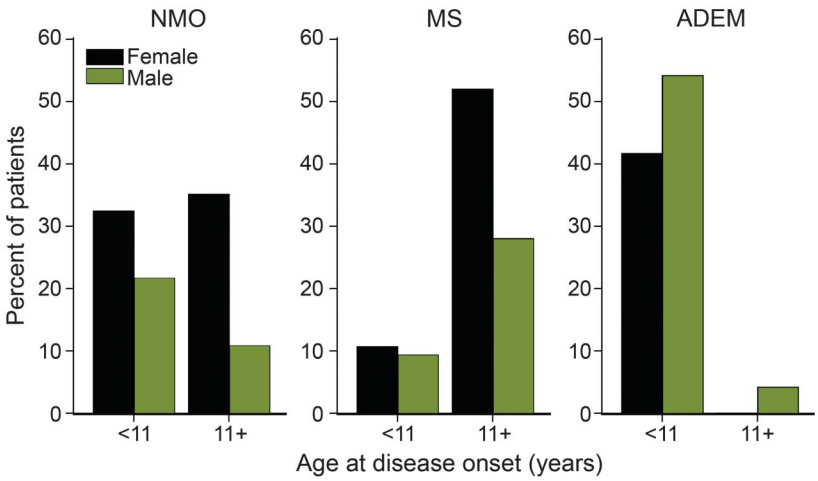
Figure 1 Age at onset in the diagnostic classification groups



Patient data are plotted on boxplots as circles randomly jittered horizontally to show density. Boxplots show the mean (diamond), first and second quartiles (shaded box), median (box center line), and fences extending to 1.5 times the interquartile range. ADEM = acute disseminated encephalomyelitis; IT = infratentorial; MS = multiple sclerosis; NMO = neuromyelitis optica; ON = optic neuritis.

(including vomiting, fever, and seizures) were the most common presenting features of NMO, and the most frequent first attack localizations were to the optic nerve, brainstem, and spinal cord (table 3). Of the NMO group, 5/38 (13%) had both spinal cord and optic nerve localization at the first event. A total of 4/5 of these patients had further attacks. We investigated the proportion of patients who presented with vomiting, since this has been identified as a first presenting symptom in adult NMO.[15] Vomiting was an initial presenting symptom in 38% of patients with NMO, as well as in 46% of patients with ADEM ($p = 0.60$ vs NMO), and in 10% of patients with MS ($p < 0.01$ vs NMO).

Figure 2 Sex distribution by age group (<11 vs ≥11 years of age) for each diagnosis classification



ADEM = acute disseminated encephalomyelitis; MS = multiple sclerosis; NMO = neuromyelitis optica.

Disease course. Time to relapse from first symptoms, number of attacks to date, and Expanded Disability Status Scale (EDSS) scores at 2 years are listed in table 3. Among patients with NMO, 2 (5%) had only one attack (onset attack); 41 (27%) patients with MS had only one attack ($p < 0.01$). Number of attacks and EDSS scores 2 years after onset were higher in NMO vs MS ($p < 0.01$ and $p = 0.02$, respectively) or ADEM ($p < 0.01$ for both comparisons). Both visual and pyramidal first symptoms scores were higher in patients with NMO than MS ($p < 0.01$ and $p = 0.06$, respectively) at 2 years.

Treatment of pediatric NMO. Median time from disease onset to disease-modifying treatment for the 34 patients with NMO with documented treatments was 286 days (IQR 95–836 days), compared to 153 days (IQR 56–391 days, $p = 0.04$ comparing NMO and MS) for the 136 patients with MS; for the 9 patients with recurrent DD-NOS with documented treatments, median time to treatment was 523 days (456–587 days, $p = 0.19$ comparing NMO and recurrent DD-NOS).

Among treatments for NMO and recurrent DD-NOS groups, rituximab (47% and 8%), mycophenolate mofetil (39% and 12%), and azathioprine (24% and 12%) were the most often reported treatments in the NMO and recurrent DD-NOS groups.

Although not considered a disease-modifying therapy in the above analysis, 39% of patients with NMO were ever treated with plasma exchange (PLEX). In the ADEM group, 2 (8%) patients were treated with PLEX; 9 (6%) of the MS group were treated with PLEX. None of the patients with DD-NOS was treated with PLEX.

Comparison of seropositive vs seronegative patients with NMO. Comparing demographic and clinical features of seropositive and seronegative NMO cases, race differed between groups ($p < 0.05$); 12/13 black/African American patients were seropositive vs 6/14 white patients and 6/10 patients with other/multiracial/unknown race. Female participants were 76% seropositive, and male participants were 42% seropositive ($p = 0.06$). No other differences were found between seropositive and seronegative NMO groups for characteristics, including age at onset, first symptoms, ON and LETM attacks, child/first-degree relative with autoimmune disease, first attack location, response to treatment, number of relapses at 2 years, or EDSS at 2 years. Presence of oligoclonal bands and mean

Table 2 Results from CSF laboratories[a]

	NMO (n = 38)		MS (n = 150)		ADEM (n = 24)	
Results from the first documented CSF test	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)
CSF leukocytes/mL[b,c]	32	105.8 (221.9)	109	19.4 (53.4)	23	55.7 (115.6)
Neutrophils	11	6.9 (12.5)	33	8.1 (11.5)	13	21.2 (22.9)
Eosinophils	12	0.8 (1.5)	26	0.6 (1.1)	7	1.4 (1.9)
Lymphocytes	25	76.2 (26.0)	90	91.4 (99.2)	18	69.4 (22.1)
Monocytes[b,c]	18	13.9 (12.8)	72	9.7 (13.3)	15	17.4 (11.4)
Positive result documented from any CSF test	No.	No. positive	No.	No. positive	No.	No. positive
Oligoclonal bands[b,c]	32	10 (31)	103	70 (68)	9	0 (0)
Elevated IgG index[b,c]	23	7 (30)	88	55 (63)	9	2 (22)

Abbreviations: ADEM = acute disseminated encephalomyelitis; IgG = immunoglobulin G; MS = multiple sclerosis; NMO = neuromyelitis optica. Values are n (%).
[a] The numbers of patients with available CSF laboratory data are shown for each measure and group. Patients with missing data are excluded from calculations of mean, SD, percent, and statistical tests.
[b] p Value <0.05 comparing NMO vs MS according to a Wilcoxon rank-sum test for continuous measures or Fisher exact test for all others.
[c] p Value <0.05 comparing NMO vs ADEM according to the tests described above (no such tests were significant).

lymphocyte, neutrophil, and eosinophil counts were similar across NMO IgG-positive vs -negative groups.

Recurrent DD-NOS. Based on the clinical characteristics, we further subclassified the recurrent DD-NOS group as (1) ADEM followed by at least one additional attack of ON (ADEM-ON) (n = 8); (2) recurrent ON attacks only (recurrent-ON) (n = 11); (3) recurrent infratentorial attacks (recurrent-IT) (n = 7). Demographic features are presented in table e-2, and first attack and clinical features are presented in tables e-1, e-3, and e-4 and figure 1. Among the recurrent DD-NOS groups, the ADEM-ON group was almost exclusively male, while the other 2 groups were predominantly female. In addition, 88% of the ADEM-ON group had onset prior to age 11 years, while recurrent-ON and recurrent-IT groups were approximately equally distributed between the age groups. The ADEM-ON group was exclusively white and non-Hispanic in the 7/8 patients who reported race. A total of 82% (9/11) of the recurrent-ON were white, and one of these patients reported Hispanic ethnicity. Of the recurrent-IT group, 71% (5/7) were white, and 2 of these patients reported Hispanic ethnicity. CSF leukocyte count (table e-1) was highest in the ADEM-ON group. In contrast, ADEM-ON had the lowest CSF lymphocyte count among the 3 groups. Notably, the recurrent DD-NOS group with recurrent IT attacks had high EDSS scores (4 ± 3.5) at 2 years.

DISCUSSION This study compares the clinical and demographic features of NMO in children with other common pediatric acquired CNS demyelinating diseases, MS and ADEM.

Although the 2006 Wingerchuk criteria had poor sensitivity for reviewer-diagnosed pediatric NMO at 49%, the revised IPND 2014 criteria were 97% sensitive. This likely reflects that children with NMO initially present with forms of disease more often consistent with the 2007 NMO-SD[11] definitions rather than with concurrent or sequential ON and transverse myelitis. Analysis of qualitative MRI features of pediatric NMO and other demyelinating diseases is underway, and will enable further sensitivity and specificity analysis. However, despite this, our reviewer classification of pediatric NMO almost fully concurred with the newly proposed IPND diagnostic criteria.

Approximately 54% of the patients with NMO were younger than 11 years at onset, compared to only 20% of the patients with MS. However, the pediatric NMO and MS sex ratio increased numerically after age 11 years in both diseases, suggesting that female preponderance increased with age and potentially as a component of puberty.[16,17]

In our study, no one demographic, first attack features collected in our database, or CSF result definitively distinguished pediatric NMO from other entities, with the exception of NMO IgG. Despite the heterogeneity of the assays used to measure serum levels at the various centers,[18] 65% of our NMO cohort was seropositive for NMO IgG, which is close to reports in adults.[18,19] NMO IgG was identified in 57% of the seropositive patients within 1 year of disease onset; however, repeat serum testing for up to 3–4 years should be considered in seronegative cases highly suspected of NMO. Early NMO IgG testing may identify the majority of pediatric NMO cases; however, enhanced assay sensitivity should be explored, particularly in the pediatric population. Among all

Table 3 First attack features and disease course 2 years following the first attack[a]

	NMO (n = 38)		MS (n = 150)		ADEM (n = 24)	
First attack features	**No.**	**Frequency (%)**	**No.**	**Frequency (%)**	**No.**	**Frequency (%)**
Location						
Optic nerve	26	17 (65)	54	36 (67)	5	2 (40)
Cerebrum[b,c]	19	6 (32)	51	47 (92)	20	20 (100)
Brainstem/cerebellar[b]	24	17 (71)	75	67 (89)	11	11 (100)
Spinal cord[b]	22	12 (55)	54	44 (81)	8	6 (75)
Symptoms						
Vision[b]	34	21 (62)	121	45 (37)	10	3 (30)
Motor	32	17 (53)	133	72 (54)	23	18 (78)
Constitutional[b]	35	23 (66)	137	49 (36)	24	21 (88)
Disease course	**No.**	**Mean (SD)**	**No.**	**Mean (SD)**	**No.**	**Mean (SD)**
Optic nerve events[b,c]	38	1.26 (1.27)	150	0.45 (0.74)	24	0.08 (0.28)
Transverse myelitis events[b,c]	38	1.26 (1.39)	150	0.57 (0.79)	24	0.25 (0.44)
First interattack period, d	35	284 (386)	109	343 (405)	0	NA
Expanded Disability Status Scale[b,c,d]	14	2.25 (1.25)	59	1.28 (1.04)	8	0.5 (0.96)
Visual Functional System Score[b,c,d]	14	2.29 (2.22)	59	0.39 (0.79)	7	0.14 (0.38)
Pyramidal Functional System Score[c,d]	14	0.79 (0.80)	59	0.44 (0.70)	8	0.13 (0.35)
No. of attacks in first 2 years[b,c,e]	38	1.84 (1.44)	150	1.03 (0.99)	24	0 (0)
Range		0–6		0–4		NA

Abbreviations: ADEM = acute disseminated encephalomyelitis; MS = multiple sclerosis; NMO = neuromyelitis optica.
[a] The numbers of patients with available data are shown for each measure and group. Patients with missing data are excluded from estimates and statistical tests.
[b] p Value <0.05 comparing NMO vs MS according to Fisher exact test (first attack features) or Wilcoxon rank-sum test (disease course).
[c] p Value <0.05 comparing NMO vs ADEM according to Fisher exact test (first attack features) or Wilcoxon rank-sum test (disease course).
[d] Expanded Disability Status Scale from the clinical visit closest to 2 years from onset, ±6 months.
[e] From the time of the first attack, not including the first attack.

contemporaneous samples, positive CSF NMO-IgG corresponded to positive serum NMO-IgG, suggesting that serum testing alone is sufficient for the majority of cases.

The number of attacks and disability level at 2 years were higher in our pediatric patients with NMO compared to pediatric MS. However, there was a delay in treatment of pediatric NMO compared to MS, which may have contributed to these differences. Nevertheless, these results indicate that prompt and effective treatment of pediatric NMO is necessary, which may be facilitated by prompt diagnosis. Similar to our findings, a study from Brazil reported persistent relapses and disability accumulation in children and adolescents with NMO despite treatment.[20] Other groups have reported high disability accrual, particularly visual disability in pediatric patients with NMO[21] and compared to adults,[4] which was influenced by race.[22] In our study, children with NMO had more frequent attacks of ON compared to MS cases, which may contribute to overall visual deficits. A French study reported slower long-term disability accrual measured by EDSS, but higher visual disability in patients with pediatric-onset NMO compared to adult-onset NMO.[23] Taken together, these results demonstrate that pediatric-onset NMO is a debilitating condition, particularly with respect to visual deficits, and further investigation into optimizing treatment strategies is required to limit disability accrual.

We identified a recurrent DD-NOS group that did not meet consensus criteria for NMO-SD or MS. This group consisted of subcategories of recurrent demyelinating disease, some of which have been noted previously in the pediatric literature.[24] Whether these cases overlap with NMO and the biological processes are similar to NMO or MS is unclear, and point to the need for further investigation into the etiology, clinical course, and response to treatment in this subgroup. Of particular concern is the subgroup with recurrent infratentorial attacks, which had a high accrual of disability at 2 years. Children with recurrent ON[25] and ADEM-ON[24] who are negative for NMO-IgG have been shown to have myelin oligodendrocyte glycoprotein (MOG) antibodies.

Strengths of our study include the multicenter prospective collection of data and the availability of

sizable comparison pediatric groups with other demyelinating CNS disorders. Limitations include the small sample size, lack of standardized MRI measures, and standardized blood testing for NMO IgG. These factors somewhat limited our ability to fully assess the 2015 IPND diagnostic criteria for NMO. Further limitations include inability to distinguish limited vs recurrent vomiting.[15] Future studies are required to assess the incidence and associations of MOG antibodies in pediatric NMO, as has been recently reported in adults,[26,27] and children with NMO.[28]

Overall, we found that the IPND 2015 criteria apply well to the pediatric setting, and given significant delay in treatment of NMO compared to pediatric MS and worse short-term outcomes, it is imperative to apply these criteria to improve access to treatment. Future work should assess response to disease-modifying treatment and promising biomarkers that may further aid in diagnosis and management of NMO in children.

AUTHOR CONTRIBUTIONS

Tanuja Chitnis: provided samples, interpretation of data, revising the manuscript, study funding. Jayne Ness: provided samples, interpretation of data, revising the manuscript. Lauren Krupp: provided samples, interpretation of data, revising the manuscript. Emmanuelle Waubant: design of study, interpretation of data, revising the manuscript. Tyler Hunt: analysis and interpretation of data, revising the manuscript. Cody S. Olsen: analysis and interpretation of data, revising the manuscript. Moses Rodriguez: provided samples, interpretation of data, revising the manuscript. Tim Lotze: provided samples, interpretation of data, revising the manuscript. Mark Gorman: provided samples, interpretation of data, revising the manuscript. Leslie Benson: data collection and revising the manuscript. Anita Belman: provided samples, interpretation of data, revising the manuscript. Bianca Weinstock-Guttman: data collection and revising the manuscript. Greg Aaen: provided samples, interpretation of data, revising the manuscript. Jennifer Graves: design of study, data collection, analysis and interpretation of data, drafting and revising the manuscript. Marc Patterson: provided samples, interpretation of data, revising the manuscript. John W. Rose: data collection, revising the manuscript. T. Charles Casper: design of study, data collection, analysis and interpretation of data, revising the manuscript.

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