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MRI Features and Their Association With Outcomes in Children With Anti-NMDA Receptor Encephalitis

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Abstract

Objectives

How brain MRI lesions associate with outcomes in pediatric anti-NMDA receptor encephalitis (pNMDARE) is unknown. In this study, we correlate T2-hyperintense MRI brain lesions with clinical outcomes in pNMDARE.

Methods

This was a multicenter retrospective cohort study from 11 institutions. Children younger than 18 years with pNMDARE were included. One-year outcomes were assessed by the modified Rankin Score (mRS) with good (mRS ≤2) and poor (mRS ≥3) outcomes.

Results

A total of 175 pNMDARE subjects were included, with 1-year mRS available in 142/175 (81%) and 60/175 (34%) had abnormal brain MRIs. The most common T2-hyperintense lesion locations were frontal, temporal, and parietal. MRI features that predicted poor 1-year outcomes included abnormal MRI, particularly T2 lesions in the frontal and occipital lobes. After adjusting for treatment within 4 weeks of onset, improvement within 4 weeks, and intensive care unit admission, MRI features were no longer associated with poor outcomes, but after multiple imputation for missing data, T2 frontal and occipital lesions associated with poor outcomes.

Discussion

Abnormal frontal and occipital lesions on MRI may associate with 1-year mRS in pNMDARE. MRI of the brain may be a helpful prognostication tool that should be examined in future studies.

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Anti-NMDA receptor encephalitis (NMDARE) causes neuropsychiatric symptoms[1,2] resulting in morbidity in 20%[3] and mortality in 10%.[4] NMDARE can be paraneoplastic, occurring in 3% of children with ovarian teratomas.[5] Management includes immunotherapy and supportive care.[6] Predicting outcomes in NMDARE are challenging, but risk factors for poor outcomes include delayed immunotherapy, younger than 2 or older than 65 years, and extreme delta brush on electroencephalography.[2] The anti-NMDA 1-Year Functional Status (NEOS) score, which includes abnormal MRI, can predict 1-year NMDARE outcomes.[7] However, in a pediatric NMDARE (pNMDARE) validation study, NEOS was applicable to the entire group, but not in an individual subject.[8]

MRI abnormalities, usually T2-hyperintense lesions, occur in one-third of children and adults with NMDARE.[1,2] Little is known about MRI features and their associated outcomes in NMDARE, especially in children. In 53 NMDARE subjects (17 of which were children), T2-hippocampal lesions associated with worse outcomes in adults, but not in children.[9] Here, we assess the association of T2-hyperintense brain MRI lesions and clinical outcomes in a multicenter pNMDARE cohort.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

A multicenter retrospective study with 11 institutions included children younger than 18 years with pNMDARE between January 1, 2008, and September 1, 2022. Diagnosis of pNMDARE was confirmed with positive CSF NMDA receptor (NMDAr) antibodies and at least 1 of 6 neuropsychiatric symptoms.[10] Institutional Review Board approval was obtained at each study site, which waived patient consent. Clinical data were collected, including outcomes using the modified Rankin Scale (mRS). NEOS scores were calculated, as a 5-point scale with 1 point for each variable: ICU admission, abnormal MRI, CSF WCC >20, treatment >4 weeks, and lack of improvement <4 weeks[7] An MRI lesion was defined as any T2-brain hyperintensity. MRI data were collected from the initial pretreatment brain MRI after neuroradiologist review for clinical purposes; then, lesion location was extracted by a neurologist at each site. Subjects with prior herpes simplex virus encephalitis were excluded. A subset of 36 subjects has been previously published.[5,8,11,12]

Statistical analysis, including descriptive statistics and comparisons, was performed as appropriate for continuous and discrete data, including for data with normal vs skewed distributions. Significance was set at $p < 0.05$ with 2-sided hypothesis testing. Multivariable regression modeling with odds ratios with 95% confidence intervals were used to calculate odds of persistent disability based on neuroimaging abnormalities. Initially, complete case analyses were performed. For sensitivity analysis, multiple imputation was performed for missing data. The variables used in the 1-year mRS outcomes to impute values included age of onset, ICU admission, treatment <4 weeks, improvement <4 weeks, and 1-year mRS scores. We also performed mediation and interaction analyses between MRI lesions and ICU admission (SAS 16.0, Cary, NC).

Data Availability

Data are available to qualified researchers based on reasonable request.

Results

Data were collected from 192 pNMDARE subjects at 11 institutions. Seventeen subjects were excluded: 5 subjects had unavailable MRI data, 7 subjects did not have confirmed CSF NMDAr antibodies, and 5 subjects had prior HSV encephalitis (Figure). A total of 175 subjects were included, with an average age of 11.6 years (SD: 5.0 years) and 70% were female (Table 1).

Thirty-four percent (60/175) had abnormal brain MRIs with the most common abnormalities including T2-hyperintense

Figure Flow Diagram of Pediatric Anti-NMDA Receptor Encephalitis Subjects Included and Excluded From This Study

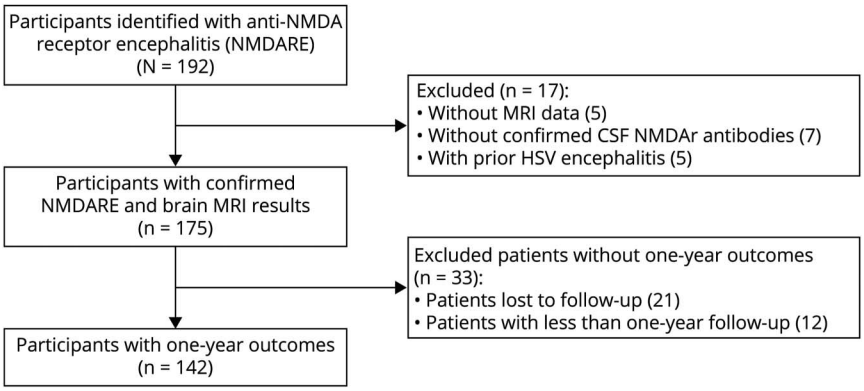

Table 1 Demographic Information for the Entire Cohort of Pediatric Anti-NMDA Receptor Encephalitis Subjects With MRI Data Available (N = 175)

	Whole cohort (N = 175)	Normal MRI (N = 115)	Abnormal MRI (N = 60)	*p* Value
Age, y, Mean (SD)	11.6 (5.0)	11.7 (4.7)	11.4 (5.5)	0.53
Sex, Female:Male, n (%)	108:47(70:30)[20]	74:34 (69:31)[7]	34:13(72:28)[13]	0.63
CSF WCC, median (IQR)	11 (4–37)[15]	9 (4–33)[11]	15.5 (5.5–38.0)[4]	0.44
CSF WCC >20, n (%)	59 (34)	35 (30)	24 (40)	0.20
CSF NMDA titers, median (IQR)	20 (13–64)[79]	20 (10–64)[56]	20 (16–40)[23]	0.29
Hospital LOS days, median (IQR)	26.0 (14,0–50.0)[14]	25.0 (13.5–46.5)[11]	29.0 (14.0–59.0)[3]	0.24
Intubation, n (%)	44 (25)	23 (20)	21 (35)	**0.030**
ICU admission, n (%)	86 (50)[2]	50 (44)[1]	37 (61)[1]	**0.032**
G-tube, n (%)	61 (36)[5]	36 (33)[5]	25 (41)	0.25
Tumor, n (%)	28 (16)[1]	18 (16)	10 (16)[1]	0.83
Abnormal EEG, n (%)	136 (80)[4]	88 (78)[2]	48 (83)[2]	0.45
Symptoms, n (%)				
Seizure	129 (76)[7]	82 (75)[6]	47 (78)	0.65
Agitation	138 (82)[7]	91 (84)[7]	47 (78)	0.34
Catatonia	60 (36)[7]	38 (35)[7]	22 (37)	0.85
Hallucinations	92 (56)[11]	61 (58)[9]	31 (53)[2]	0.61
Hypoventilation	23 (14)[8]	13 (12)[7]	10 (17)[1]	0.39
Movement disorder	114 (67)[6]	77 (71)[6]	37 (62)	0.23
Speech changes	140 (84)[9]	89 (83)[8]	51 (86)[1]	0.58
Suicidal ideation	13 (8)[14]	8 (8)[10]	5 (9)[4]	0.77
Treatment, n (%)				
IV steroids	164 (93)	106 (92)	58 (97)	0.25
IVIG	162 (93)[1]	107 (94)[1]	55 (92)	0.75
PLEX	75 (43)[2]	45 (39)[1]	30 (51)[1]	0.15
Second-line	132 (76)[2]	87 (77)[2]	45 (75)	0.77
Rituximab	130 (75)[1]	85 (75)[1]	45 (75)	0.95
Cyclophosphamide	22 (13)[1]	13 (11)[1]	9 (15)	0.50
MMF	11 (6)[4]	5 (5)[4]	6 (10)	0.20
Other	6 (4)[8]	4 (4)[7]	2 (3)[1]	1.0
MRI brain T2 lesion location, n (%)				
Hippocampus	11 (6)	0 (0)	11 (18)	—
Parietal	21 (12)	0 (0)	21 (35)	—
Thalamus	9 (5)	0 (0)	9 (15)	—
Temporal	28 (16)	0 (0)	28 (47)	—
Pons	2 (1)	0 (0)	2 (3)	—
Occipital	7 (4)	0 (0)	7 (12)	—
Midbrain	3 (2)	0 (0)	3 (5)	—

Continued

Table 1 Demographic Information for the Entire Cohort of Pediatric Anti-NMDA Receptor Encephalitis Subjects With MRI Data Available (N = 175) *(continued)*

	Whole cohort (N = 175)	Normal MRI (N = 115)	Abnormal MRI (N = 60)	*p* Value
Medulla	3 (2)	0 (0)	3 (5)	—
Frontal	31 (18)	0 (0)	31 (52)	—
Basal ganglia	10 (6)	0 (0)	10 (17)	—
Other MRI findings, n (%)				
Atrophy present	7 (4)	0 (0)	7 (12)	—
MRI leptomeningeal enhancement	14 (8)	0 (0)	14 (23)	—
MRI parenchymal enhancement	17 (10)	0 (0)	17 (28)	—
Outcomes				
Time to treatment, median (IQR)	15 (9–26)[39]	14 (9–26)[20]	15.5 (8.0–28.0)[18]	0.16
Treatment before 4 wk, n (%)	108 (79)[38]	76 (80)[20]	32 (76)[18]	0.62
Improve <4 wk, n (%)	86 (51)[7]	54 (49)[5]	32 (55)[2]	0.44
Time to improvement, days, median (IQR)	17 (8–31)[61]	17 (8–35)[38]	16.5 (7.0–28.0)[22]	0.16
NEOS, mean (SD)	2.5 (1)[40]	2.1 (0.9)[20]	3.6 (1.1)[19]	**<0.0001**
NEOS, n (%)				
0	2 (1)	2 (2)	0 (0)	—
1	25 (18)	23 (24)	2 (5)	—
2	44 (32)	41 (43)	3 (7)	—
3	38 (28)	22 (23)	16 (39)	—
4	17 (13)	7 (7)	10 (24)	—
5	10 (7)	0 (0)	10 (24)	—
mRS poor at 1 y, n (%)	29 (20)[33]	14 (15)[14]	15 (29)[9]	**0.047**
mRS = 0 at 1 y, n (%)	35 (25)[33]	27 (30)[14]	8 (16)[8]	0.064
mRS poor at 2 y, n (%)	14 (13)[67]	7 (10)[47]	7 (18)[20]	0.29
mRS = 0 at 2 y, n (%)	39 (36)[67]	29 (43)[47]	10 (25)[20]	0.065

Abbreviations: EEG = electroencephalography; G-tube = gastrostomy tube; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; mRS = modified Rankin Score; NEOS = anti-NMDA 1-year functional status score; WCC = white cell count.
Bolded values are $p < 0.05$.
[a] Number of participants with missing data.

frontal (31/60 = 52%), temporal (28/60 = 47%), and parietal (21/60 = 35%) lesions (Table 1). Abnormal brain MRI was associated with ICU admission, intubation, higher NEOS score, and poor 1-year mRS (mRS ≥3) scores.

For 1-year outcomes, 142 participants had available data, with poor (mRS ≥3) outcomes in 29 and 113 had good (mRS ≤2) outcomes (Table 2). Abnormal brain MRI correlated with poor 1-year outcomes (OR 2.9; 95% CI 1.2–7.0), as did frontal (OR 4.2; 95% CI 1.5–11.6) and occipital lobe T2-hyperintense lesions (OR 6.8; 95% CI 1.1–43.3). Other variables associated with poor 1-year outcomes included prolonged hospital length of stay, intubation, ICU admission, gastrostomy placement, plasma exchange and/or second-line treatments (including rituximab and cyclophosphamide), and no improvement <4 weeks from symptom onset (Table 2). Data from 12 patients were not included because 1 year had not passed from symptom onset. We also assessed those lost to 1-year follow-up by assessing faster recovery or milder disease by comparing mRS at 3 and 6 months or improvement <4 weeks. No differences were observed in these characteristics between those included vs excluded at the 1-year follow-up.

Using multivariable logistic regression, adjusting for ICU admission, improvement <4 weeks, and treatment <4 weeks, abnormal MRI, T2 frontal, and T2 occipital lesions no longer

Table 2 Demographic Information for the Cohort of Pediatric Anti-NMDA Receptor Encephalitis Subjects With Available 1-Year Outcomes Assessed by Modified Rankin Score (mRS) (N = 143)

	Entire cohort (N = 142)	Good (N = 113)	Poor (N = 29)	*p* Value
Age, y, mean (SD)	11.7 (4.9)	11.9 (4.6)	10.4 (5.7)	0.12
Sex, Female:Male, n (%)	39 (31)[16]	30 (29)[11]	9 (36)[5]	0.52
CSF WCC, median (IQR)	10 (4–37)[7]	10 (4–32)[4]	14 (4–40)[3]	0.63
CSF WCC >20, n (%)	46 (32)	34 (30)	12 (41)	0.25
CSF NMDA titers, median (IQR)	20 (10–64)[59]	20 (10–64)[45]	20 (10–80)[14]	0.86
Hospital LOS days, median (IQR)	24 (13–49)[10]	21 (12–46)[7]	43.5 (17–61)[3]	**0.04**
Intubation, n (%)	34 (24)	19 (17)	15 (52)	**<0.0001**
ICU admission, n (%)	69 (49)	46 (41)	23 (79)	**0.0002**
G-tube, n (%)	48 (35)[4]	27 (25)[3]	21 (75)[1]	**<0.0001**
Tumor, n (%)	18 (13)[1]	11 (10)[1]	7 (24)	0.058
Abnormal EEG, n (%)	108 (78)[3]	83 (75)[2]	25 (89)[1]	0.21
Symptoms, n (%)				
Seizure	107 (78)[4]	84 (76)[3]	23 (82)	0.51
Agitation	110 (80)[5]	85 (78)[4]	25 (89)[1]	0.18
Catatonia	46 (33)[4]	33 (30)[3]	13 (46)[1]	0.10
Hallucinations	74 (55)[7]	63 (59)[6]	11 (39)[1]	0.064
Hypoventilation	18 (13)[6]	14 (13)[4]	4 (15)[2]	0.79
Movement disorder	89 (64)[4]	67 (61)[3]	22 (79)[1]	0.08
Speech changes	117 (85)[5]	109 (79)[4]	25 (89)[1]	0.77
Suicidal ideation	10 (7)[8]	9 (8)[7]	1 (3)[1]	0.69
Treatment, n (%)				
IV steroids	132 (93)	105 (93)	27 (93)	1.00
IVIG	132(93)	103 (91)	29 (100)	0.21
PLEX	60 (42)	39 (35)	21 (72)	**0.0002**
Second-line	109 (77)[1]	81 (72)[1]	28 (97)	**0.006**
Rituximab	107 (75)	79 (70)	28 (97)	**0.003**
Cyclophosphamide	19 (13)	7 (6)	12 (41)	**<0.0001**
MMF	11 (8)[3]	10 (9)[2]	1 (4)[1]	0.46
Other	6 (4)[5]	3 (3)[3]	3 (11)[2]	0.091
MRI brain T2 lesion location, n (%)				
Abnormal brain MRI	51 (36)	36 (32)	15 (52)	**0.047**
Hippocampus	10 (7)	6 (5)	4 (14)	0.12
Parietal	18 (13)	11 (10)	7 (24)	0.057
Thalamus	8 (6)	5 (4)	3 (10)	0.36
Temporal	23 (16)	17 (15)	6 (21)	0.57
Pons	2 (1)	1 (1)	1 (3)	0.37
Occipital	7 (5)[1]	3 (3)[1]	4 (14)	**0.033**

Continued

Table 2 Demographic Information for the Cohort of Pediatric Anti-NMDA Receptor Encephalitis Subjects With Available 1-Year Outcomes Assessed by Modified Rankin Score (mRS) (N = 143) *(continued)*

	Entire cohort (N = 142)	Good (N = 113)	Poor (N = 29)	*p* Value
Midbrain	3 (2)	1 (1)	2 (7)	0.11
Medulla	3 (2)	2 (2)	1 (3)	0.50
Frontal	27 (19)	17 (15)	10 (35)	**0.017**
Basal ganglia	9 (6)	6 (5)	3 (10)	0.39
Other MRI findings, n (%)				
Atrophy present	7 (5)[1]	3 (3)	4 (14)[1]	**0.029**
MRI leptomeningeal enhancement	12 (8)	9 (8)	3 (10)	0.71
MRI parenchymal enhancement	17 (12)	12 (11)	5 (17)	0.34
Outcomes				
Time to treatment, median (IQR)	15 (9–25)[29]	15 (9–28)[22]	17 (7–23)[7]	0.12
Treatment before 4 wk, n (%)	89 (77)[29]	71 (78)[22]	18 (82)[8]	1.00
Improve <4 wk, n (%)	70 (52)[7]	61 (56)[5]	9 (33)[2]	**0.031**
Time to improvement, days, median (IQR)	6 (8–34)[47]	14 (7–27)[37]	34 (13–66)[10]	0.52
NEOS, mean (SD)	2.5 (1.2)[29]	2.4 (1.2)[22]	2.8 (1.1)[7]	0.17
NEOS, n (%)[29]				
0	2 (2)	2 (2)	0 (0)	—
1	22 (19)	19 (21)	3 (14)	—
2	36 (32)	30 (33)	6 (27)	—
3	31 (27)	25 (27)	6 (27)	—
4	14 (12)	8 (9)	6 (27)	—
5	8 (7)	7 (8)	1 (5)	—
mRS = 0 at 1 y, n (%)	35 (25)	35 (31)	0 (0)	—
mRS poor at 2 y, n (%)	14 (13)[34]	2 (2)[29]	12 (50)[5]	—
mRS = 0 at 2 y, n (%)	39 (36)[34]	39 (46)[29]	0 (0)[5]	—

Abbreviations: EEG = electroencephalography; G-tube = gastrostomy tube; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; mRS = modified Rankin Score; NEOS = anti-NMDA 1-year functional status score; WCC = white cell count.
Bolded values are $p < 0.05$.
[a] Number of participants with missing data.

associated with poor outcomes; ICU admission was the only predictor for poor outcomes (eTable 1, links.lww.com/NXI/A860). Interaction and mediation analyses of ICU admission did not affect the relationship between MRI lesions and outcomes. Sensitivity analyses were performed using multiple imputation to fill in missing data for 1-year mRS outcomes in 33 patients, with missing mRS scores (23), missing treatment <4 weeks (8), missing ICU admission (1), and missing ICU admission/treatment <4 weeks (1). After multiple imputation, T2 frontal (OR 2.81, 95% CI 1.10–6.66) and occipital lobe lesions (OR 8.58, 95% CI 1.15–64.3) were associated with poor 1-year outcomes, even when adjusting for ICU admission, treatment <4 weeks, and improvement <4 weeks (eTable 2).

Discussion

In this pNMDARE cohort, abnormal brain MRI was associated with poor 1-year outcomes, particularly T2-hyperintense frontal and occipital lesions. Abnormal brain MRIs were also associated with intubation and ICU admission. This is one of the largest studies to date that examines T2-hyperintense lesion locations and their association with outcomes in pNMDARE.

Despite multiple neurologic symptoms, only 34% of pNMDARE had brain MRI abnormalities. As executive dysfunction and impulsivity are common residual symptoms in NMDARE,[1] T2-hyperintense frontal lobe lesions may help to identify those at

higher risk for long-term neuropsychological dysfunction. Residual memory problems are also common, but T2-hippocampal/temporal lesions did not associate with outcomes in this study. Surprisingly, T2-hyperintense occipital lobe lesions associated with poor outcomes but may be due to other brain involvement. Although ICU admission altered the associations of MRI lesions with 1-year outcomes and ICU admission did not have a mediation or interaction effect, multiple imputation did demonstrate an association between T2 frontal and occipital lesions with outcomes. This suggests that missing data are affecting the results, which were mitigated by multiple imputation. Moreover, T2 lesions may overlap with demyelinating diseases[13] and/or reflect cytotoxic injury, suggestive of more severe disease and affect outcomes.

Limitations include that we performed a descriptive and retrospective study of MRI lesion location without including lesion volume or networks. Multiple observers inputted MRI data, which could introduce bias. Another limitation includes that we cannot confirm that all T2-hyperintense lesions present on acute imaging are related to NMDARE as prior MRIs are unavailable. The timing of MRI from symptom onset or its relationship to the number of abnormalities was not included, which may confound this study. In those without 1-year mRS scores, many of these subjects had not reached 1-year follow-up time and our subjects lost to follow-up appeared random. Compounding this, data were collected from tertiary and quaternary pediatric medical centers, and thus, severity bias and convenience sampling are present in this data set. This could affect the rates of neuroimaging abnormalities and 1-year disability. Finally, mRS was used as a standardized and efficient outcome measure that is consistent across institutions; however, the mRS may not adequately capture residual cognitive/neuropsychiatric symptoms in NMDARE.[1,14,15]

T2-hyperintense frontal and occipital lobe lesions may associate with poor outcomes in pNMDARE. Future studies should also explore the association of MRI lesions, their locations, and networks with residual neuropsychological outcomes.

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Disclosure

G.Y. Gombolay, J.N. Brenton, J.H. Yang, C.M. Stredny, R. Kammeyer, C. Otten, N. Vu, J.D. Santoro, K. Robles-Lopez, A. Christiana, C. Steriade, M, Morris, M. Gorman, M. Moodley, D. Hardy, A. Kornbluh, I. Kahn, and L. Sepeta have no relevant disclosures. A. Yeshokumar is an employee of Bristol Myers Squibb but does not affect this study. Go to Neurology.org/NN for full disclosures.

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Grace Gombolay, MD	Emory University SOM and Children's Healthcare of Atlanta	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
J. Nicholas Brenton, MD	University of Virginia Health System	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Jennifer H. Yang, MD, PhD, MAS	University of California San Diego and Rady Children's Hospital San Diego	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
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Ryan Kammeyer	University of Colorado SOM and Children's Hospital Colorado	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
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NgocHanh Vu, MD	Vanderbilt University Medical Center	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
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Karla Robles-Lopez, MD	University of Texas at Austin and Dell Medical School	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Andrew Christiana, MD	New York University SOM	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
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Mark Gorman, MD	Boston Children's Hospital and Harvard Medical School	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Manikum Moodley, MD	University of Texas at Austin and Dell Medical School	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Duriel Hardy, MD	University of Texas at Austin and Dell Medical School	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Alexandra B. Kornbluh, MD	Children's National Hospital and George Washington University Medical School	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Ilana Kahn, MD	Children's National Hospital and George Washington University Medical School	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

Appendix *(continued)*

Name	Location	Contribution
Leigh N. Sepeta, PhD	Children's National Hospital and George Washington University Medical School	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Anusha Yeshokumar, MD	Mount Sinai University and Bristol Myers Squibb	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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