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Familial History of Autoimmune Disorders Among Patients With Pediatric Multiple Sclerosis

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Abstract

Background and Objective

The objective of this study was to determine whether family members of patients with pediatric multiple sclerosis (MS) have an increased prevalence of autoimmune conditions compared with controls.

Methods

Data collected during a pediatric MS case-control study of risk factors included information about various autoimmune diseases in family members. The frequency of these disorders was compared between cases and controls.

Results

There was an increased rate of autoimmune diseases among family members of pediatric MS cases compared with controls with first-degree history of MS excluded (OR = 2.27, 95% CI 1.71–3.01, $p < 0.001$). There was an increased rate of MS among second-degree relatives of pediatric MS cases compared with controls (OR = 3.47, 95% CI 1.36–8.86, $p = 0.009$). The OR for MS was 2.64 when restricted to maternal relatives and 6.37 when restricted to paternal relatives.

Discussion

The increased rates of autoimmune disorders, including thyroid disorders and MS among families of patients with pediatric MS, suggest shared genetic factors among families with children diagnosed with pediatric MS.

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Glossary

MS = multiple sclerosis.

Multiple sclerosis (MS) is an autoimmune disorder targeting the CNS that is most commonly diagnosed in women around age 30 years.[1] An estimated 5% of all MS cases have onset under age 18 years.[2] Multiple genetic and environmental risks have been identified for MS.[1] Studying pediatric MS provides a unique opportunity to gain insights into the pathophysiology and causes of MS because of the relatively fewer number of irrelevant exposures preceding disease onset and the possibility that larger exposures result in earlier onset.

Genetic risk factors for pediatric MS have been reported that overlap with adult MS. These include *HLA-DRB1*15:01* and multiple class III risk variants.[3] Several risk factors for autoimmune disorders, including genetic variants or vitamin D deficiency, are shared among various conditions, including MS.[4-10] There have been conflicting reports about rates of autoimmune diseases in families of patients with adult MS.[11,12] Data consistently, however, note that MS risk is increased among first-degree relatives of patients with MS, including children of parents with MS.[13] This study sought to understand the incidence of a history of autoimmune diseases in family members of pediatric MS cases compared with pediatric controls.

Methods

Participants of this case-control study included children with MS or clinically isolated syndrome and healthy pediatric subjects recruited at 17 clinics participating as part of a nationwide study of environmental risk factors in pediatric MS between November 1, 2011, and July 1, 2017 (R01NS071463, PI Waubant). Diagnosis and control status was established by the treating neurologist and confirmed by adherence to published criteria for pediatric demyelinating disease as determined by a panel of 3 pediatric MS specialists using the 2010 McDonald Criteria. Centers obtained institutional review board approval as well as written informed consent from parents of pediatric participants and assent as appropriate from children. Criteria mandated that cases were enrolled within 4 years of symptom onset. Healthy controls were recruited from primary care, urgent care, or other pediatric clinics at the participating institutions. Eligibility criteria for controls required (1) absence of any ongoing autoimmune disease (apart from eczema and asthma) and (2) no history of MS in any immediate, biological family member. Demographic data including race and ethnicity, consistent with NIH guidelines, were provided by parents of pediatric participants. Standardized medical history questionnaires were completed by patients and families including family autoimmune disease history.

All analyses were conducted using SAS 9.4 (SAS Institute; Cary, NC). Patient characteristics were summarized using medians and quartiles or counts and percentages as appropriate. Chi-squared tests were used to compare reported family history of autoimmune disease between cases and controls, for both overall history of any disease and for specific diseases (e.g., MS).

Logistic regression models were used to test for differences between cases and controls in reporting a family history of autoimmune diseases, when adjusting for sex, race, age, ethnicity, and mother's education level. ORs and 95% CIs were calculated based on the logistic regression models.

The diseases that were found to be significant in the overall tests were investigated within 5 relative groups: first-degree relatives, second-degree relatives, parents, maternal relatives,

Table 1 Subject Characteristics

	Subject status as case or control		
	Control (N = 709)	Case (N = 495)	*p* Value
Age at enrollment: median (Q1, Q3)	15.6 (12.5, 17.8)	16.0 (14.2, 17.5)	0.196[b]
Sex			0.052[a]
Male	290 (40.9%)	175 (35.4%)	
Female	419 (59.1%)	320 (64.6%)	
Race			0.115[a]
White	438 (61.8%)	311 (62.8%)	
Black	107 (15.1%)	87 (17.6%)	
Other	114 (16.1%)	60 (12.1%)	
Unknown	50 (7.1%)	37 (7.5%)	
Ethnicity			<0.001[a]
Hispanic or Latino	155 (21.9%)	150 (30.3%)	
Not Hispanic or Latino	519 (73.2%)	318 (64.2%)	
Unknown	35 (4.9%)	27 (5.5%)	
Mother's education level			<0.001[a]
None	40 (5.6%)	51 (10.3%)	
High school or associate's	294 (41.5%)	244 (49.3%)	
Bachelor's or graduate	292 (41.2%)	138 (27.9%)	
Unknown	83 (11.7%)	62 (12.5%)	

Statistical tests exclude missing or unknown values.
[a] Chi-squared test of no association.
[b] Wilcoxon rank-sum test.

Table 2 Unadjusted Analyses of Reported Family History of Autoimmune Disease

	Subject status as case or control		
	Control (N = 709)	Case (N = 495)	*p* Value
Any reported family history[a]	351 (49.5%)	337 (68.1%)	<0.001[b]
Diabetes: adult onset	211 (29.8%)	221 (44.6%)	<0.001[b]
Diabetes: childhood onset	19 (2.7%)	31 (6.3%)	0.002[b]
Thyroid disease/Hashimoto disease/Graves disease	95 (13.4%)	99 (20.0%)	0.002[b]
Rheumatoid arthritis	66 (9.3%)	77 (15.6%)	<0.001[b]
MS[a]	29 (4.1%)	68 (13.7%)	<0.001[b]
Atopic dermatitis/eczema	45 (6.3%)	24 (4.8%)	0.271[b]
Psoriasis	36 (5.1%)	26 (5.3%)	0.892[b]
Inflammatory bowel disease/ Crohn disease/ulcerative colitis	25 (3.5%)	29 (5.9%)	0.054[b]
Systemic lupus erythematosus	22 (3.1%)	28 (5.7%)	0.029[b]
Other autoimmune disease	72 (10.2%)	69 (13.9%)	0.045[b]

Abbreviation: MS = multiple sclerosis.
Celiac disease, hyperparathyroidism, Sjogren syndrome, rheumatic heart disease, sarcoidosis, idiopathic thrombocytopenic purpura, vitiligo, mixed connective tissue disease, scleroderma, pernicious anemia, ankylosing spondylitis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome, myasthenia gravis, pemphigus vulgaris, vasculitis, Addison disease, polymyositis, Bechet syndrome, and polyarteritis nodosa were grouped with the other autoimmune disease category.
[a] Excludes first-degree history of MS.
[b] Chi-squared test of no association.

Table 3 Adjusted Analyses of Reported Family History of Autoimmune Disease

	OR (95% CI)	*p* Value
Any reported family history[a]	2.27 (1.71, 3.01)	<0.001
Diabetes: adult onset	1.80 (1.37, 2.35)	<0.001
Diabetes: childhood onset	2.26 (1.22, 4.22)	0.010
Thyroid disease/Hashimoto disease/ Graves disease	1.72 (1.22, 2.43)	0.002
Rheumatoid arthritis	1.63 (1.11, 2.38)	0.012
MS[a]	4.16 (2.57, 6.75)	<0.001
Atopic dermatitis/eczema	0.89 (0.52, 1.51)	0.656
Psoriasis	1.08 (0.63, 1.84)	0.792
Inflammatory bowel disease/Crohn disease/ulcerative colitis	1.95 (1.09, 3.47)	0.024
Systemic lupus erythematosus	2.16 (1.16, 4.01)	0.015
Other autoimmune disease	1.35 (0.92, 1.99)	0.129

Abbreviation: MS = multiple sclerosis.
Results are based on models adjusting for age, sex, race, ethnicity, and biological mother's highest level of education.
[a] Excludes first-degree history of MS.

and paternal relatives. The same statistical methods applied to the overall analyses were implemented in the relative group analyses. When expected cell counts were less than 5, Fisher exact tests were performed in place of χ^2 tests. A significance level of 0.05 was used for all analyses.

Data Availability

Deidentified data sets from this study can be made available to qualified investigators with appropriate ethics/IRB approval. Data are stored for up to 5 years postpublication.

Results

Participants' Characteristics

This study included 1,204 participants with 709 controls and 495 cases (37 of which were categorized as clinically isolated syndrome). The breakdown of cases and controls based on age, sex, race, and ethnicity is summarized in Table 1. Groups were well matched except for ethnicity and mother's education.

Family History of Autoimmune Disorders

Because controls could not have a history of MS in immediate biological family members (study exclusion criteria), analyses involving familial MS excluded first-degree relatives. There was a significant difference in prevalence of a family history of autoimmune disease in patients with MS compared with controls (68.1% vs 49.5%, $p < 0.001$) (Table 2). The conditions with significant differences in prevalence between cases and controls were childhood-onset and adult-onset diabetes, thyroid disorders, rheumatoid arthritis, MS (in non–first-degree relatives), and systemic lupus erythematosus. Significant differences between cases and controls were also found for the "other" category. Rates of eczema, psoriasis, and bowel disorders did not differ significantly. With adjusted analyses (adjusted for age, sex, race, ethnicity, and biological mother's highest level of education), the OR of any family history of autoimmune disease was 2.27 among cases compared with controls (95% CI, 1.71–3.01, $p < 0.001$) (Table 3). With adjusted analyses, the OR of any family history of MS (in non–first-degree relatives) was 4.16 among cases compared with controls (95% CI, 2.57–6.75, $p < 0.001$) (Table 3). Furthermore, with the adjusted analyses, the other category of autoimmune diseases lost statistical significance while inflammatory bowel diseases were more prevalent in families of patients with pediatric MS ($p = 0.024$).

Separate analyses were performed to understand the association between family history of autoimmune diseases and pediatric MS based on which relatives were reported as having autoimmune diseases. The analysis was performed for several categories of relatives: all first-degree relatives, just parents, second-degree relatives, maternal relatives, and paternal relatives. History of MS in pediatric MS patient's mothers was excluded from the maternal relative analysis for MS, and history of MS in patient's fathers was excluded from the

Table 4 Analyses of Reported History of Autoimmune Disease Within Various Relative Groups

			Unadjusted analyses	Adjusted analyses[c]	
	Control (N = 709)	Case (N = 495)	*p* Value	OR (95% CI)	*p* Value
First-degree relatives					
Diabetes: adult onset	44 (6.2%)	48 (9.7%)	0.025[a]	1.41 (0.88, 2.28)	0.156
Diabetes: childhood onset	4 (0.6%)	9 (1.8%)	0.038[a]	1.80 (0.50, 6.50)	0.369
Thyroid disease/Hashimoto disease/Graves disease	47 (6.6%)	52 (10.5%)	0.016[a]	1.73 (1.10, 2.72)	0.018
Rheumatoid arthritis	9 (1.3%)	16 (3.2%)	0.019[a]	2.52 (1.04, 6.10)	0.040
Inflammatory bowel disease/Crohn disease/ulcerative colitis	12 (1.7%)	11 (2.2%)	0.509[a]	1.49 (0.64, 3.47)	0.352
Systemic lupus erythematosus	5 (0.7%)	7 (1.4%)	0.249[b]	2.58 (0.70, 9.52)	0.155
Other autoimmune disease	30 (4.2%)	26 (5.3%)	0.408[a]	1.14 (0.62, 2.07)	0.675
Second-degree relatives					
Diabetes: adult onset	144 (20.3%)	160 (32.3%)	<0.001[a]	1.88 (1.41, 2.51)	<0.001
Diabetes: childhood onset	6 (0.8%)	10 (2.0%)	0.080[a]	2.83 (0.92, 8.69)	0.070
Thyroid disease/Hashimoto disease/Graves disease	41 (5.8%)	31 (6.3%)	0.730[a]	1.06 (0.63, 1.80)	0.822
Rheumatoid arthritis	38 (5.4%)	45 (9.1%)	0.012[a]	1.73 (1.07, 2.79)	0.024
MS	8 (1.1%)	15 (3.0%)	0.018[a]	3.47 (1.36, 8.86)	0.009
Inflammatory bowel disease/Crohn disease/ulcerative colitis	6 (0.8%)	10 (2.0%)	0.080[a]	2.39 (0.84, 6.86)	0.104
Systemic lupus erythematosus	8 (1.1%)	9 (1.8%)	0.318[a]	1.58 (0.58, 4.31)	0.373
Other autoimmune disease	30 (4.2%)	31 (6.3%)	0.114[a]	1.35 (0.78, 2.35)	0.290
Parents					
Diabetes: adult onset	44 (6.2%)	48 (9.7%)	0.025[a]	1.41 (0.88, 2.28)	0.156
Diabetes: childhood onset	0 (0.0%)	2 (0.4%)	0.169[b]	-[d]	-[d]
Thyroid disease/Hashimoto disease/Graves disease	47 (6.6%)	46 (9.3%)	0.088[a]	1.49 (0.93, 2.37)	0.096
Rheumatoid Arthritis	9 (1.3%)	15 (3.0%)	0.031[a]	2.34 (0.95, 5.75)	0.063
Inflammatory bowel disease/Crohn disease/ulcerative colitis	8 (1.1%)	10 (2.0%)	0.210[a]	2.01 (0.77, 5.24)	0.152
Systemic lupus erythematosus	5 (0.7%)	5 (1.0%)	0.749[b]	1.77 (0.43, 7.32)	0.430
Other autoimmune disease	27 (3.8%)	24 (4.8%)	0.378[a]	1.14 (0.61, 2.14)	0.688
Maternal relatives					
Diabetes: adult onset	132 (18.6%)	138 (27.9%)	<0.001[a]	1.61 (1.19, 2.17)	0.002
Diabetes: childhood onset	2 (0.3%)	10 (2.0%)	0.005[b]	8.71 (1.87, 40.43)	0.006
Thyroid disease/Hashimoto disease/Graves disease	80 (11.3%)	76 (15.4%)	0.039[a]	1.53 (1.05, 2.21)	0.025
Rheumatoid arthritis	45 (6.3%)	51 (10.3%)	0.013[a]	1.51 (0.97, 2.36)	0.068
MS[a]	20 (2.8%)	32 (6.5%)	0.002[a]	2.64 (1.43, 4.89)	0.002
Inflammatory bowel disease/Crohn disease/ulcerative colitis	12 (1.7%)	14 (2.8%)	0.182[a]	1.83 (0.82, 4.07)	0.137
Systemic lupus erythematosus	15 (2.1%)	16 (3.2%)	0.229[a]	1.97 (0.92, 4.26)	0.083
Other autoimmune disease	49 (6.9%)	50 (10.1%)	0.047[a]	1.32 (0.84, 2.09)	0.230

Continued

Table 4 Analyses of Reported History of Autoimmune Disease Within Various Relative Groups *(continued)*

			Unadjusted analyses	Adjusted analyses[c]	
	Control (N = 709)	Case (N = 495)	*p* Value	OR (95% CI)	*p* Value
Paternal relatives					
Diabetes: adult onset	86 (12.1%)	104 (21.0%)	<0.001[a]	1.87 (1.33, 2.63)	<0.001
Diabetes: childhood onset	6 (0.8%)	11 (2.2%)	0.046[a]	2.88 (1.04, 7.97)	0.042
Thyroid disease/Hashimoto disease/Graves disease	17 (2.4%)	20 (4.0%)	0.104[a]	1.80 (0.90, 3.63)	0.098
Rheumatoid arthritis	15 (2.1%)	26 (5.3%)	0.003[a]	2.92 (1.44, 5.91)	0.003
MS[e]	9 (1.3%)	35 (7.1%)	<0.001[a]	6.37 (2.97, 13.66)	<0.001
Inflammatory bowel disease/Crohn disease/ ulcerative colitis	7 (1.0%)	13 (2.6%)	0.029[a]	3.60 (1.32, 9.84)	0.012
Systemic lupus erythematosus	5 (0.7%)	8 (1.6%)	0.132[a]	2.42 (0.75, 7.85)	0.140
Other autoimmune disease	20 (2.8%)	19 (3.8%)	0.326[a]	1.33 (0.66, 2.69)	0.425

Abbreviation: MS = multiple sclerosis.
[a] Chi-squared test of no association.
[b] Fisher exact test.
[c] Adjusted analyses are based on logistic models adjusting for age, sex, race, ethnicity, and biological mother's highest level of education.
[d] The logistic regression model for childhood-onset diabetes reported in subject's parents was not stable as none of the controls reported parents with childhood-onset diabetes.
[a] Excludes history of MS in mothers as controls with first-degree history of MS are excluded from the study.
[e] Excludes history of MS in fathers as controls with first-degree history of MS are excluded from the study.

paternal relative analysis for MS, as controls could not have a history of MS in either parent. Adjusted analyses revealed an OR of 3.47 of MS among second-degree relatives of patients with pediatric MS. The OR was 2.64 when restricted to maternal relatives and 6.37 when restricted to paternal relatives (Table 4). Adjusted analyses revealed that there was a statistically significant difference between cases and controls in prevalence of adult-onset diabetes, childhood-onset diabetes, and MS in both maternal and paternal secondary relatives. Rheumatoid arthritis and inflammatory bowel disease had a higher prevalence in paternal second-degree relatives, but not maternal. In contrast, thyroid disorders had a higher prevalence in maternal second-degree relatives, but not paternal.

Discussion

We sought to identify the prevalence of familial autoimmune disorders in pediatric MS compared with controls as most studies have focused on adult MS.[12] As children who develop MS 20–30 years earlier than average age at onset likely have larger genetic burden and/or environmental exposures than adults with the disease, the prevalence of autoimmune disorders in their family may be higher than reported for adults with MS. Studies of a familial history of autoimmune disease in patients with adult MS have yielded conflicting results.[14,15]

We have identified a number of autoimmune conditions with increased prevalence among the family members of patients with pediatric MS. Of note, 13.7% of patients with pediatric MS reported a familial history of MS compared with only 4.1% of controls (for whom parents could not have the disease as specified by study exclusion criteria). In another study, 25.5% of patients with adult MS reported a family history of MS compared with only 4.1% of controls.[14] There were significant differences between cases and controls relative to the frequency of autoimmune diseases (e.g., diabetes and rheumatoid arthritis), suggesting some shared risk factors for these conditions. Indeed, prior work has suggested shared genetic variants across several autoimmune disorders.[15]

Notably, not all autoimmune conditions followed this pattern. There was no increase in the odds of psoriasis and eczema among family members of pediatric MS cases compared with controls.

Presumably, the link between various autoimmune diseases might be genetic and/or environmental exposures that trigger an aberrant immune response. Although various autoimmune diseases differ in their target organs and antigens, they share a common loss of self-tolerance. When analyzing the rate of familial autoimmune diseases, especially among non–first-degree relatives, an increased risk of autoimmune conditions would likely be caused by shared genetic risk factors, rather than environmental exposures. Understanding families with increased rates of autoimmune conditions could provide an opportunity for dissecting out the universal genetic risks for autoimmunity separate from the genetic risk factors associated with single conditions. This study found that there was a higher rate of MS in second-degree relatives among the patients with pediatric MS compared with controls, and this difference was most pronounced when the history of MS was

paternal. Risk of various autoimmune diseases based on parent of origin has been described in numerous genetics studies, with some conditions having maternal associations (e.g., Crohn and juvenile idiopathic arthritis) and others having paternal associations (e.g., psoriatic arthritis).[16,17]

Strengths of the study include the prospective collection of data in multiple centers in the United States representing various geographical areas, careful case ascertainment, and the number of pediatric patients recruited. In addition, controls were enrolled at the same institutions than cases. Weaknesses include the survey-based format of data collection (i.e., the lack of medical confirmation of autoimmune disorders reported by families) and the potential for a biased sampling of controls since recruitment occurred at academic pediatric hospitals and clinics. There are risks for both under- and over-reporting of family history and the possibility of recall bias among cases. Although recall bias could definitely lead to an overestimation of autoimmune diseases in the case cohort, the fact that several conditions were found to have no statistical difference between cases and control reduces the bias concern.

The higher rate of autoimmune diseases among family members of patients with pediatric MS compared with controls, especially the higher rate of MS in second-degree relatives among the patients with pediatric MS, supports the possibility of shared genetic variants between several autoimmune diseases and MS. The higher rate of specific disorders among paternal relatives raises the question of possible imprinting. The rate of autoimmune disease in this control cohort was higher than the general population, particularly in terms of the percent of participants reporting adult onset diabetes within their family (i.e., 29%). This represents a potential bias to the conclusions that could skew the significance of the findings, but not likely change the overall conclusion. Future studies could be designed to compare the genetic profiles of various pediatric autoimmune disorders in an attempt to determine disease specific genes separate from the genes that dictate risk of losing self-tolerance. Combining cohort and family history diagnostic data with expanded genotyping could help establish relative risk of autoimmunity in families based on genetic predispositions. This would require expanded genotyping programs beyond traditional trio designed genetic studies.

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Soe S. Mar, MD	Washington University, St. Louis, MO	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Jayne M. Ness, MD	University of Alabama Birmingham	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Patricia Plumb, RN	The University of Texas Southwestern, Department of Neurology, Dallas	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Shannon Liang, MD	Department of Radiology, Washington University in St. Louis, MO	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data

Appendix *(continued)*

Name	Location	Contribution
Manu Goyal, MD	Department of Radiology, Washington University in St. Louis, MO	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Bianca Weinstock-Guttman, MD	Jacobs Pediatric Multiple Sclerosis Center, State University of New York at Buffalo	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and study concept or design
Moses Rodriguez, MD	Mayo Clinic Pediatric Multiple Sclerosis Center, Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
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John W. Rose, MD	Department of Neurology, University of Utah, Salt Lake City	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Mark P. Gorman, MD	Pediatric Multiple Sclerosis and Related disorders Program, Boston Children's Hospital	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Leslie A. Benson, MD	Pediatric Multiple Sclerosis and Related disorders Program, Boston Children's Hospital	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Meghan Candee, MD, MSc	Primary Children's Hospital, University of Utah, Salt Lake City	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
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Appendix *(continued)*

Name	Location	Contribution
Yolanda C. Harris, MSN, CRNP	Center for Pediatric-Onset Demyelinating Disease, Children's Hospital of Alabama, University of Alabama	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Ilana L. Kahn, MD	Children's National Medical Center, WA, DC	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Shelly Roalstad, MS	Data Coordinating and Analysis Center, University of Utah, Salt Lake City	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Janace Hart, BA	Pediatric Multiple Sclerosis Center, University of California San Francisco, CA	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Timothy E. Lotze, MD	The Blue Bird Circle Clinic for Multiple Sclerosis, Texas Children's Hospital, Baylor College of Medicine, Houston	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Mary Rensel, MD	Mellen Center for Multiple Sclerosis, Cleveland Clinic, Cleveland, OH	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Jennifer P. Rubin, MD	Lurie Children's Hospital of Chicago, Chicago, IL	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Teri L. Schreiner, MD, MPH	Rocky Mountain Multiple Sclerosis Center, Children's Hospital Colorado, University of Colorado at Denver, Aurora	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Jan-Mendelt Tillema, MD	Mayo Clinic Pediatric Multiple Sclerosis Center, Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Amy Tara Waldman, MD, MAS	Children's Hospital of Philadelphia, PA	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Lauren Krupp, MD	Pediatric Multiple Sclerosis Center, New York University	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Jennifer Graves, MD, PhD	Pediatric Multiple Sclerosis Center, University of California San Diego	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Kaylea Drake, MS	Data Coordinating and Analysis Center, University of Utah, Salt Lake City	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Emmanuelle Waubant, MD	Pediatric Multiple Sclerosis Center, University of California San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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