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Collaborative International Research in Clinical and Longitudinal Experience Study in NMOSD

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Abstract

Objective

To develop a resource of systematically collected, longitudinal clinical data and biospecimens for assisting in the investigation into neuromyelitis optica spectrum disorder (NMOSD) epidemiology, pathogenesis, and treatment.

Methods

To illustrate its research-enabling purpose, epidemiologic patterns and disease phenotypes were assessed among enrolled subjects, including age at disease onset, annualized relapse rate (ARR), and time between the first and second attacks.

Results

As of December 2017, the Collaborative International Research in Clinical and Longitudinal Experience Study (CIRCLES) had enrolled more than 1,000 participants, of whom 77.5% of the NMOSD cases and 71.7% of the controls continue in active follow-up. Consanguineous relatives of patients with NMOSD represented 43.6% of the control cohort. Of the 599 active cases with complete data, 84% were female, and 76% were anti-AQP4 seropositive. The majority were white/Caucasian (52.6%), whereas blacks/African Americans accounted for 23.5%, Hispanics/Latinos 12.4%, and Asians accounted for 9.0%. The median age at disease onset was 38.4 years, with a median ARR of 0.5. Seropositive cases were older at disease onset, more likely to be black/African American or Hispanic/Latino, and more likely to be female.

Conclusions

Collectively, the CIRCLES experience to date demonstrates this study to be a useful and readily accessible resource to facilitate accelerating solutions for patients with NMOSD.

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GJCF-ICC Coinvestigators are listed in Appendix 2.

Glossary

AQP4 = aquaporin-4; **ARR** = annual relapse rate; **CRC** = Clinical Research Coordinator; **EDSS** = Expanded Disability Status Scale; **GJCF** = The Guthy-Jackson Charitable Foundation; **ICC** = International Clinical Consortium; **IQR** = interquartile range; **MOG** = myelin oligodendrocyte glycoprotein; **NMOSD** = neuromyelitis optica spectrum disorder; **PSF** = patient study file.

Neuromyelitis optica spectrum disorder (NMOSD) represents a chronic, potentially debilitating and life-threatening neuroinflammatory process primarily targeting the optic nerves, spinal cord, and brain.[1–4] The typical clinical course of NMOSD is marked by multiple relapses resulting in cumulative neurologic disabilities. These events are interspersed with remissions from disease activity of variable duration. Heightened awareness of the disease among health care providers and the public and recent advances in diagnostic precision have increased estimates of worldwide NMOSD prevalence, reaching as high as 10 per 100,000 in some populations.[5–8] This projection translates to more than 15,000 patients with NMOSD in the United States, suggesting that hundreds of thousands of cases exist worldwide. NMOSD disproportionately affects females (up to 7:1 female-to-male ratio), with anti-aquaporin-4 (AQP4) antibody (hereafter referred to as anti-AQP4) positive disease having even greater propensity for women.[9,10] Yet, many details regarding etiology, pathogenesis, risk factors, and demography of NMOSD are in need of greater understanding.

Although case series and observational studies suggest benefit from immunotherapy, to date no treatment of NMOSD has been proven safe and effective in prospective, double-masked and adequately powered clinical trials.[11–13] Because of its rarity, insufficient access to well-characterized patient cohorts has historically hindered studies as has an absence of high-fidelity preclinical models of human disease. Limitations in carefully standardized, longitudinal clinical research tools have also impeded investigation of NMOSD immunopathogenesis. However, 4 separate clinical trials have now reported positive results evaluating 3 compounds (eculizumab, satralizumab, and inebilizumab) in studies assessing efficacy in delaying or preventing relapses in NMOSD.

The Guthy-Jackson Charitable Foundation (GJCF) initiated an observational study of NMOSD in which patients and comparative controls are enrolled and evaluated longitudinally in a standardized manner. This study, known as Collaborative International Research in Clinical and Longitudinal Experience Studies (CIRCLES) for NMOSD, was launched in November 2013. In CIRCLES, participant clinical data, demographic profiles, and biospecimens were collected at geographically dispersed academic medical centers located throughout North America (figure 1).

The design and performance of the CIRCLES study are described here, along with initial data analysis illustrating the utility of its database and biorepository to advance scientific knowledge and clinical care in NMOSD. It is anticipated that this study will accelerate greater understanding of NMOSD and in turn the development of safe and effective therapies to benefit patients with NMOSD and perhaps those diagnosed with other autoimmune diseases.

Methods

Clinical research standards

Human subjects protection

Participant enrollment is conducted in accordance with the guidelines specified by the Office of Human Research Protections of the US Food and Drug Administration. A standardized protocol, manual of operations, patient study file (PSF), and informed consent or assent documents were approved by the institutional review board of each participating institution. Written and verbal consent or assent was obtained before beginning study procedures. The protocol and PSF were updated periodically.

Study goals and design

Design

CIRCLES is a prospective, multicenter, cross-sectional, and longitudinal study enabling comparisons of NMOSD cases and controls from which clinical data and biospecimens were collected using standardized methods. These were collected from cases at 6-month intervals and at least annually from control participants. When possible, clinical data and biospecimens were obtained from cases during or within 10 days following clinically confirmed relapses.

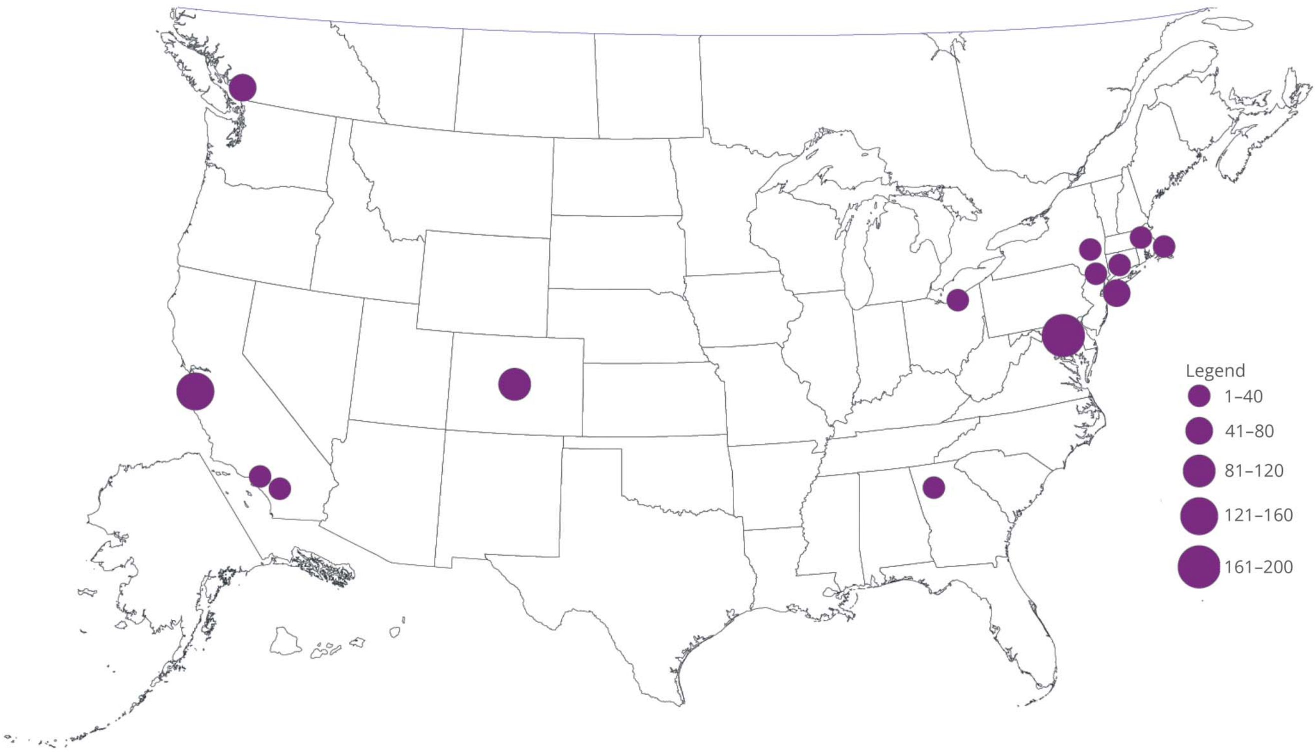
Goals

Two primary goals of CIRCLES include the following: (1) establish a cohort of patients with NMOSD and comparative controls who are longitudinally assessed at standardized intervals and (2) analyze acquired clinical data and biospecimens, thus improving knowledge of NMOSD and the patient experience.

Sites

Multiple study sites were established at academic institutions throughout North America (figure 1), each led by a clinical investigator/neurologist with expertise in NMOSD. Study sites were selected based on the size/activity of their NMOSD

Figure 1 Geographic location of CIRCLES clinical sites



patient cohort and capability to collect data and biospecimens in the protocol-defined manner. Biospecimens, predominantly peripheral blood constituents, are rapidly transferred to a centralized commercial laboratory for processing and archiving.

Cohorts

The study comprises 3 participant cohorts based on the following inclusion criteria: (1) cases with clinically diagnosed NMOSD according to either the Wingerchuk 2006[14] or International Panel for NMOSD Diagnosis 2015[14] criteria and classified with respect to anti-AQP4 serostatus; (2) comparative disease controls (including CNS autoimmune diseases [e.g., MS]; other autoimmune diseases [e.g., systemic lupus erythematosus, Sjögren syndrome, and type I diabetes mellitus]; chronic nonautoimmune inflammatory or systemic conditions [e.g., cardiovascular disease and type 2 diabetes]); and (3) healthy controls (i.e., those not carrying a chronic disease diagnosis at enrollment). Controls included consanguineous relatives and unrelated individuals (tables 1 and 2). Enrollment is targeted to a 2:1 ratio of cases to controls and is monitored centrally. Individuals (both cases and controls) are excluded if the treating physician feels that they are not appropriate for the study. Control participants are not sex or age matched. Some comparative disease controls are recruited from referral cohorts (e.g., MS). Others are recruited through opportunity or convenience. Sites are instructed to enroll control participants at a rate of 50% MS and 50% from the other categories.

Intervals

After enrollment, NMOSD cases are evaluated clinically at 6-month intervals to provide an updated clinical history and complete set of biospecimens. Control participants undergo these same assessments at least annually. The panel of biospecimens routinely collected is listed in supplemental table 1 (links.lww.com/NXI/A121). The protocol allows collection of CSF and additional tissues (e.g., placenta) as available from medically indicated care. Relapses are evaluated regardless of interval and adjudicated by site neurologists.

Participating cohorts

Eligibility

Individuals fulfilling inclusion criteria and absent exclusion criteria are eligible for enrollment. Individuals weighing <17 kg are excluded from blood collections but may otherwise participate.

Enrollment

Clinical research coordinators (CRCs) screen information pertaining to inclusion and exclusion criteria. Individuals receive study information through mail and/or social media and, where institutional review board-approved, have the

Table 1 Summary of case participant characteristics by serostatus

	Overall[a] (N = 599)	NMO-IgG status: Negative (N = 139)	NMO-IgG status: Positive (N = 449)	*p* Value
Female	504 (84.1%)	102 (73.4%)	393 (87.5%)	<0.001[g]
Participant primary ethnicity/race designation				<0.001[g]
Asian	54 (9.0%)	17 (12.2%)	37 (8.2%)	
Black or African American	141 (23.5%)	16 (11.5%)	125 (27.8%)	
Hispanic or Latino	74 (12.4%)	13 (9.4%)	60 (13.4%)	
White	315 (52.6%)	87 (62.6%)	218 (48.6%)	
Other	15 (2.5%)	6 (4.3%)	9 (2.0%)	
Not reported	0 (0%)	0 (0%)	0 (0%)	
Age at consent	47.1 (36.0–57.2)	43.3 (29.8–52.3)	48.6 (37.7–59.1)	<0.001[h]
Age at first episode onset[b]	38.4 (28.9–50.6)	35.1 (25.8–46.4)	39.4 (29.9–52.5)	0.002[h]
Relapse/year from disease onset to most recent visit[c]	0.5 (0.3–0.8)	0.5 (0.3–0.9)	0.4 (0.3–0.8)	0.031[h]
Time (y) from first episode onset to enrollment[b]	4.6 (1.5–10.1)	3.8 (1.4–7.0)	4.9 (1.5–11.0)	0.008[h]
Longitudinally extensive transverse myelitis[d]	396 (66.1%)	83 (59.7%)	305 (67.9%)	0.064[g]
Optic neuritis[f]	395 (65.9%)	102 (73.4%)	286 (63.7%)	0.038[g]
Brainstem syndrome[f]	155 (25.9%)	40 (28.8%)	111 (24.7%)	0.346[g]
Focal transverse myelitis[e]	143 (23.9%)	46 (33.1%)	94 (20.9%)	0.004[g]
Area postrema syndrome[f]	88 (14.7%)	20 (14.4%)	66 (14.7%)	0.920[g]
Cerebral syndrome[f]	74 (12.4%)	20 (14.4%)	53 (11.8%)	0.425[g]
Diencephalic syndrome[f]	23 (3.8%)	7 (5.0%)	15 (3.3%)	0.360[g]

Abbreviation: NMO = neuromyelitis optica.
[a] Eleven case participants have undetermined serostatus.
[b] Age at first episode onset and time from first episode onset to enrollment not recorded on 6 participants.
[c] Relapses per year from disease onset to most recent visit not recorded on 32 participants because of insufficient follow-up or missing data.
[d] Longitudinally extensive transverse myelitis not recorded on 3 participants.
[e] Focal transverse myelitis not recorded on 4 participants.
[f] Optic neuritis, brainstem syndrome, area postrema syndrome, cerebral syndrome, and diencephalic syndrome not recorded on 2 participants.
[g] χ^2 test of association.
[h] Wilcoxon rank-sum test.

option to provide preliminary information telephonically with consent obtained in advance of study participation. At enrollment, a thorough review of medical records and clinical examination is performed by the study neurologist. A complete disease history and additional relevant study data are collected during the initial interview (table e-3, links.lww.com/NXI/A121). The majority of participants to date have been enrolled coinciding with medically indicated appointments; however, in some cases, enrollment was conducted per protocol at patient-oriented educational events.

Clinical database

Clinical metadata

The CIRCLES PSF (table e-2, links.lww.com/NXI/A121) is completed for each participant at enrollment and updated at each follow-up study visit. The PSF data include demographics, disease phenotype, treatment history, and other relevant characteristics. Other than NMOSD disease history, identical clinical data are collected as appropriate from case and healthy control participants.

Data security

Data are entered into a web-accessible and password-secured electronic data capture system. The CIRCLES study incorporates a query management system that executes nightly. An email notification is generated for each site's CRC identifying any new discrepant data. A weekly reminder email is also provided for remaining discrepant data. The system tracks queries from generation to resolution. Data are curated for quality, consistency, and completeness by the Data Coordinating Center biostatistics group before archiving. Study data are backed up hourly, and a full snapshot of the study is archived nightly.

Table 2 Summary of control participant characteristics by relatedness to NMOSD cases

	Case blood relative (N = 123)	Unrelated (N = 95)	Total (N = 218)
Female	73 (59.3%)	71 (74.7%)	144 (66.1%)
Race[a]			
Asian	9 (7.3%)	8 (8.4%)	17 (7.8%)
Black or African American	8 (6.5%)	13 (13.7%)	21 (9.6%)
Hispanic or Latino	20 (16.3%)	16 (16.8%)	36 (16.5%)
White	81 (65.9%)	56 (58.9%)	137 (62.8%)
Other	4 (3.3%)	2 (2.1%)	6 (2.8%)
Age at consent (y)	44.9 (34.2–53.9)	50.9 (38.9–58.3)	47.1 (35.9–56.2)
Comparative disease			
MS	37 (30.1%)	0 (0.0%)	37 (17.0%)
CNS autoimmune disease other than MS	10 (8.1%)	0 (0.0%)	10 (4.6%)
Systemic autoimmune disease	5 (4.1%)	14 (14.7%)	19 (8.7%)
CNS disorder unrelated to an inflammatory disease	4 (3.3%)	1 (1.1%)	5 (2.3%)
Systemic chronic condition	3 (2.4%)	4 (4.2%)	7 (3.2%)
None of the above	69 (56.1%)	78 (82.1%)	147 (67.4%)

Abbreviation: NMOSD = neuromyelitis optica spectrum disorder.
[a] Race not recorded on 1 participant.

Biospecimen repository

Collection, processing, and storage

Biospecimens are collected according to standard operating procedures at enrollment and follow-up visits. A panel of blood specimens is obtained (table e-1, links.lww.com/NXI/A121) by routine venipuncture by a certified phlebotomist at each scheduled clinical visit. Biospecimens are transported by express courier to a commercial laboratory for processing, systematic labeling, and archiving within 24 hours of collection under certified storage conditions (liquid nitrogen for peripheral blood mononuclear cells and −80°C for sera, plasma, RNA, and DNA).

Quality and serostatus

Biospecimens are routinely assessed for quality postprocessing and before cryopreservation. Autoantibody serostatus is determined by the respective study site based on reference laboratory assay or review of the case record. For analytical purposes, seropositivity is defined as having detected anti-AQP4 at any point during the participant's history.

Statistical analysis

Analytical range

The current report encompasses data sets obtained from 2013 through 2017. The CIRCLES study is ongoing.

Analytical methods

Descriptive statistics (medians or interquartile ranges [IQRs] for numeric variables; counts and percentages for categorical variables) were used to analyze data. Wilcoxon rank-sum tests were used to assess relationships between age at disease onset, annualized relapse rate (ARR) during enrollment in the study, and time between the first and second attacks in relation to other demographic characteristics in NMOSD cases. Relationships between serostatus and race, serostatus and sex, and race and sex were examined using χ^2 tests. All analyses were performed in SAS 9.4 (Cary, NC).

Data availability

Access to data and biospecimens is provided to qualified scholars in a peer-reviewed process. Applications are adjudicated by a biorepository oversight committee elected from among the members of the GJCF International Clinical Consortium (ICC).

Results

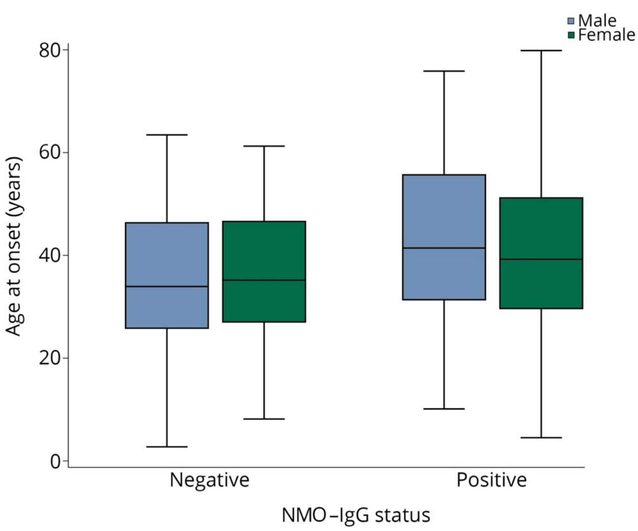
Study enrollment

As of December 2017, CIRCLES had enrolled 849 NMOSD cases and 339 controls, of which 658 (77.5%) and 243 (71.7%), respectively, continue to participate. The percentage of enrollees remaining active has increased over time. Of the 161 participants enrolled in 2013, 49.7% are still active. This compares to 73.7% of those enrolled in 2014, 67.9% in 2015, 74.4% in 2016, and 90.8% in 2017. Inability to contact accounted for most inactivity (74%), followed by withdraw of consent (14%), no longer able to participate (9%), and death (2%). Of all participants, 60.3%, 31.3%, and 8.4% were enrolled at study sites, national patient day events, and regional patient day events, respectively. In-clinic enrollees, compared with national and regional patient day enrollees, were more likely to remain active (89.7% vs 55.1% and 74.5%, respectively). The size of the enrolled cohort varied among study sites, with the largest site enrolling 286 (24.1%) of all participants and the smallest enrolling 20 (1.7%). Among active NMOSD cases, 495 (75.2%) have undergone one or more follow-up visits with biospecimen collection. Among active controls, 129 (53.1%) had one or more follow-up visits and biospecimen collection. The remainder of the analyses presented are based on these active cases and control participants who have complete data as of the end of the study period.

Cohort demographics and epidemiology

In the CIRCLES cohort, the female-to-male ratio was 5.3:1 among cases (tables 1 and 2). NMOSD cases self-identified as white/Caucasian (52.6%), 23.5% black/African American, 12.4% Hispanic/Latino, 9.0% Asian, and 2.5% from all other races/ethnicities. The overall median age at NMOSD onset was 38.4 years (IQR 28.9–50.6 years), appears to be normally distributed, and spans the range from 2.7 to 79.9 years (figure 2). The median time between disease onset and time to study enrollment was 4.6 years (IQR 1.5–10.1 years). CIRCLES cases experienced an ARR of 0.5 (IQR 0.3–0.9). One hundred thirty-two cases appear to be monophasic. For cases with ≥2 clinically documented NMOSD relapses (n = 207), the median time between the first and second attacks was 0.8 years (9 months; IQR 3.3–27.9). The most common relapse manifestations were longitudinally extensive transverse myelitis (≥2 vertebral segments; 396, 66.1%) and optic neuritis (395, 65.9%). Brainstem syndromes were identified in 155 (25.9%) cases, 143 (23.9%) manifested focally confined transverse myelitis, 88 (14.7%) area postrema syndrome (e.g., prolonged or intractable nausea/vomiting or hiccups), 74 (12.4%) cerebral syndrome (cognitive and/or sensory impairment, pain, bowel and/or bladder dysfunction, or limb weakness), and 23 (3.8%) diencephalic and/or brainstem syndromes (facial numbness, hearing loss, dysphagia, or dysarthria) (table 1).

Figure 2 Age at onset by serostatus and gender



Biospecimen repertoire

Of the active NMOSD cases, 193 (32.2%) provided a single set of biospecimens; 2 longitudinal sets were collected from 151 (25.2%) cases, 3 sets from 107 (17.9%), and 4 or more from 131 (21.9%). Of the active controls, 102 (46.8%) provided a single biospecimen set, 65 (29.8%) 2 sets, 26 (11.9%) 3 sets, and 21 individuals (9.6%) have provided 4 or more longitudinal samples.

Correlation analyses

Bioinformatic analyses have revealed several significant correlates in the CIRCLES cohort (table 1). Anti-AQP4 seropositive cases were more likely to be female (87.5%) compared with seronegative cases (73.4%, $p < 0.001$). Significant differences in racial distribution by serostatus ($p < 0.001$) were also detected. This result was driven largely by differences in the black/African American and white race categories. Although black/African American participants accounted for only 11.5% of the seronegative population, they comprise 27.8% of seropositive cases. Similarly, Hispanic/Latino cases represent only 9.4% of seronegative cases, but 13.4% of seropositive cases. Conversely, white/Caucasian cases account for 62.6% of seronegative cases, but less than half (48.6%) of the seropositive cases. Similarly, Asians account for a higher percentage of the seronegative population (12.2%) compared with the seropositive population (8.2%).

Overall, seropositive cases are older at initial NMOSD attack compared with seronegative participants (39.4 vs 35.1; $p = 0.002$; figure 2). White/Caucasian and Asian cases tend to be older at first attack compared with black/African Americans or Hispanics (41.1 and 38.3 vs 36.5 and 36.0, $p < 0.001$; table 3). Seropositive cases tend to have lower ARR than those who are seronegative (0.46 vs 0.55; $p = 0.030$). No significant differences were detected between race and ARR ($p = 0.34$).

Of the 218 control participants, 95 (43.6%) are consanguineous with an enrolled case. One hundred forty-four (66.1%) are female. The median age of controls at enrollment was 47.1 years. Of the related controls, none have MS, 17.9% have another autoimmune disease, and 82.1% have no comparative disease or chronic condition. Of the unrelated controls, 28.5% have MS, 15.4% have another autoimmune disease, and 56.1% have no comparative disease or condition (table 2).

Discussion

The CIRCLES study represents a unique and multicenter longitudinal observational study, which has successfully recruited and retained a large number of patients affected by the rare disease NMOSD. The substantial number of control participants who are consanguineous with enrolled cases also provides important new opportunities to understand disease resilience. In this respect, individuals with familial genotypes and environmental exposures, but who do not manifest NMOSD, can be evaluated in relation to patients with NMOSD. In addition, the CIRCLES project reflects the collaborative input of the GJCF-ICC, a global network of scientific and medical experts in NMOSD.

The demographic characteristics of the CIRCLES cohort to date are comparable to those of previously described NMOSD registries.[13,15–22] Interesting relationships have emerged from initial demographic, epidemiologic, and correlational analyses of this cohort. Key relationships include identification of correlations between disease attributes and sex, age, and race. NMOSD cases are predominantly female (5.3:1) and anti-AQP4 seropositive (76.4%). Disease onset most commonly occurs in the fourth decade of life. These findings are congruent with recent epidemiologic studies of NMOSD regarding sex predominance, age at onset, and disease clustering in individuals and their first-degree relatives.[5,23–25]

Analysis of the CIRCLES cohort supports the concept that a sizable proportion of cases satisfying either 2006 or 2015 diagnostic criteria for NMOSD[14,26] includes individuals in whom anti-AQP4 is not detected. Approximately 20.6% of female and 39.8% of male cases in CIRCLES are anti-AQP4 seronegative, representing a significant difference based on sex ($p < 0.001$). Whether such proportions accurately reflect anti-AQP4 serostatus worldwide, correlate with specific disease phenotypes, or inform regarding response to therapy remains uncertain. Key among the proximate determinants of this serostatus are anti-AQP4 assay sensitivities and specificities. For example, it is possible that therapies inadvertently affect selection bias (e.g., rituximab targeting B cells). However, no consistent evidence published to date has proven these therapies alter antibody detection in Clinical Laboratory Improvement Amendments–approved assays. Seropositive cases are more likely to be female, and self-identified black/African American or Hispanic/Latino patients are more likely to be anti-AQP4 seropositive, congruent with earlier reports.[5] Furthermore, cases in which anti-AQP4 is detected are older at first attack than those who are seronegative (39.4 vs 35.1, respectively, $p = 0.002$). Although white/Caucasian cases accounted for nearly 63% of the anti-AQP4 seronegative cohort, they account for less than 50% of seropositive cases. The age at first attack also differed by race, with a nearly 5-year disparity between the median age at onset for Hispanics/Latinos compared with white/Caucasians. This finding could reflect socioeconomic skewing of access to specialized medical care, a difference in disease activity/severity, other factor(s), or a combination of factors.

Of note, the prevalence of NMOSD appears to differ in distinct geographic regions. For example, the current estimate of NMOSD prevalence is 3.9 per 100,000 in Olmsted County, Minnesota (USA),[5] similar to that reported in Denmark (4 per 100,000[27]). In contrast, the prevalence ranges from 0.72 per 100,000 in England,[28] 0.89 per 100,000 in Spain,[7] and 0.9 per 100,000 in Japan[6] to 1.96 per 100,000 in Wales,[29] 2.5 per 100,000 in the French West Indies,[30] 2.6 per 100,000 in India,[31] and as high as 10 per 100,000 in Martinique.[5] It is possible that differences in diagnostic criteria could underlie at least some of these apparent differences. In any event, the current CIRCLES data offer insights extending those provided by recent reviews.[8,32]

The sizable proportion of cases in which anti-AQP4 is not detected suggests that the NMOSD phenotype can result from multiple, independent immunologic events. The emerging recognition of individuals with phenotypes resembling NMOSD, but in whom anti-myelin oligodendrocyte glycoprotein (anti-MOG) autoantibodies are detected in the absence of anti-AQP4,[10,33,34] suggests at least 2 intriguing possibilities: (1) a broader array of autoantigens than traditionally appreciated may contribute to astrocytopathies and/or (2) patients having anti-MOG autoantibodies may reflect a disease entity that is immunologically distinct from NMOSD, despite largely superimposable clinical manifestations. Thus, patients with anti-MOG antibodies may exhibit disease features that are pathogenically distinct from NMOSD, despite their similar clinical presentations.[34,35]

Table 3 Case demographic factors by race and ethnicity

	N	Female (N = 599)	Age at onset (N = 593)	ARR (N = 593)
White	315	253 (80.3%)	41.1 (31.1–53.0)	0.5 (0.3–0.9)
Black or African American	141	130 (92.2%)	36.5 (26.1–45.5)	0.5 (0.3–0.9)
Hispanic or Latino	74	67 (90.5%)	36.0 (22.6–46.5)	0.5 (0.3–1.0)
Asian	54	43 (79.6%)	38.3 (25.2–50.2)	0.4 (0.2–0.7)
Other	15	11 (73.3%)	31.7 (22.2–43.1)	0.5 (0.2–0.9)
***p* Value**	—	0.005[a]	<0.001[b]	0.342[b]

Abbreviation: ARR = annualized relapse rate.
[a] χ^2 test of association.
[b] Analysis of variance.

Nevertheless, 1 recent epidemiologic study showed that individuals with detectable anti-MOG antibody had similar disease prevalence and long-term prognosis when compared with patients lacking detectable anti-AQP4 or anti-MOG antibody.[10] Thus, the relationship between serology and disease phenotype remains to be more clearly understood.

As with all large, multicenter clinical research studies, there are limitations to CIRCLES. Some participants inconsistently followed up or provided incomplete historical information. Complete acquisition of PSF data elements, biospecimens, and fully documented neurologic examination data has proven challenging. In turn, acquiring disability data from incomplete neurologic examinations has emerged as a high priority for improvement. For example, although 90.9% of examinations included completed motor function assessments, only 49.5% assessed visual acuity, and 8.7% completed the Expanded Disability Status Scale. The study has not systematically monitored anti-MOG serostatus,[16] as no approved clinical assay for this autoantibody existed during the study period.

A unique aspect of CIRCLES concerns the detailed clinical history captured at enrollment. For those whose disease is of long duration, recall bias is possible. Beyond basic clinical data, the CIRCLES PSF requests extensive retrospective clinical information, including history of infectious diseases, vaccinations, familial autoimmune diseases, medications, and treatments. Although collection of such extensive information is labor intensive, the resulting data set enables interrogations not possible from smaller or less comprehensive databases. Opportunities for enhancing study performance are currently being addressed through refinements of the study protocol. In particular, increased emphasis has been placed on longitudinal participation, more frequent site monitoring, and systematic methods for disseminating information to study sites pertaining to study performance and efficiency.

The design of CIRCLES allows direct comparisons between the clinical courses of NMOSD and other autoimmune diseases, informing key immunologic events unique to NMOSD. These events in turn facilitate identification of clinically useful biomarkers, including those heralding disease relapse, as well as novel therapeutic targets, agents, and strategies. The CIRCLES biobank contains clinical information and biospecimens from ethnically and geographically diverse cases, including those with heterotypic phenotypes. Thus, CIRCLES represents a unique resource to the academic and drug-discovery communities focused on finding solutions for patients with NMOSD and may enhance parallel efforts in other immune-based diseases.

In summary, areas of research urgently needed in NMOSD include discovery of disease etiology, identification of risk factors, and identification of biomarkers reflecting disease activity and predicting relapse.[36,37] The ongoing CIRCLES continues to enroll and follow cases and categorical control participants in a systematic and longitudinal manner. This effort is intended to facilitate breakthroughs regarding the epidemiology and pathogenesis of NMOSD, to reduce barriers to performing well-designed therapeutic trials, and to support postapproval studies of eventually approved therapeutics. Thus, the overarching goal of CIRCLES is to improve patient quality of life through improved diagnosis, relapse prevention, and eventual cures.[38–40]

The CIRCLES program enables unprecedented opportunities to accelerate breakthroughs in scientific understanding and clinical solutions for NMOSD. Key to the future applicability of CIRCLES will be increased precision in diagnosis and uniformity in the assessment and specification of distinct disease phenotypes. These advances hinge on greater consistency of serologic analysis regarding autoantibodies specific to disease phenotype and standardization in the definition and severity scoring of NMOSD relapses. As these advances are made, they will be incorporated into the definitions used by CIRCLES, attesting to the evolving nature of this research platform. CIRCLES remains an open resource to facilitate hypothesis generation and testing. Given the nature of the biospecimens being collected, CIRCLES enables studies ranging from genomics, transcriptomics, proteomics, and other molecular- and cellular-based research, in addition to clinical investigation.

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Disclosure

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Appendix 1 *(continued)*

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Appendix 1 *(continued)*

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Continued

Appendix 1 *(continued)*

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Appendix 1 *(continued)*

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Appendix 2 *(continued)*

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Continued

Appendix 2 *(continued)*

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Name	Location	Role	Contribution
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Naraporn Prayoonwiwat, MD	Division of Neurology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand	Coinvestigator	Reviewed and revised the manuscript for intellectual content.
Anne-Katrin Pröbstel, MD	Neurologic Clinic and Policlinic, Departments of Medicine, and Biomedicine, University Hospital, University of Basel, Basel, Switzerland; UCSF Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco, San Francisco, CA	Coinvestigator	Reviewed and revised the manuscript for intellectual content.
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Appendix 2 *(continued)*

Name	Location	Role	Contribution
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Victor Rivera, MD	Baylor College of Medicine, Houston, TX	Coinvestigator	Reviewed and revised the manuscript for intellectual content.
Dalia L. Rotstein, MD	University of Toronto, Department of Medicine, Division of Neurology	Coinvestigator	Reviewed and revised the manuscript for intellectual content.
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Appendix 2 *(continued)*

Name	Location	Role	Contribution
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