Neuromyelitis optica spectrum disorder

Patient experience and quality of life

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Abstract

Objective
To gain insights into NMOSD disease impact, which may negatively affect QoL of patients, their families, and social network.

Methods
The current study used validated instruments to assess physical, emotional, and socioeconomic burden of NMOSD on QoL among 193 patients.

Results
A majority of patients reported an initial diagnosis of a disease other than NMOSD. Overall, two-thirds of patients reported NMOSD as having a strong negative impact on physical health (Short Form-36 [SF-36] score 27.1 ± 39.1), whereas emotional well-being was relatively unimpaired on average (SF-36 score 54.0 ± 44.9). A subset of patients reported having the highest category of emotional health despite worse physical health or financial burden, suggesting psychological resilience. Pain (r = 0.61) and bowel/bladder dysfunction (r = 0.41) imposed the greatest negative physical impact on overall QoL. In turn, ability to work correlated inversely with worsened health (r = −0.68). Increased pain, reduced sexual function, inability to work, and reduced QoL had greatest negative impacts on emotional well-being. Dissatisfaction with treatment options and economic burden correlated inversely with QoL.

Conclusions
Collectively, the current findings advance the understanding of physical, emotional, social, and financial tolls imposed by NMOSD. These insights offer potential ways to enhance QoL by managing pain, enhancing family and social networks, and facilitating active employment.

Glossary

ANOVA = analysis of variance; **AQP4** = aquaporin-4; **GJCF** = Guthy-Jackson Charitable Foundation; **MOG** = myelin oligodendrocyte glycoprotein; **NMO** = neuromyelitis optica; **NMOSD** = neuromyelitis optica spectrum disorder; **QoL** = quality of life; **SF-36** = Short Form-36.

Neuromyelitis optica spectrum disorder (NMOSD) is a potentially life-threatening neuroinflammatory disease targeting the optic nerve, spinal cord, and brain.[1–4] Relapses result in cumulative neurologic disabilities, are unpredictable, and are interspersed with remissions. Increased diagnostic accuracy and increased health care provider awareness have resulted in increased prevalence up to 10/100,000 in some geographic regions.[5–8] This estimate equates to >15,000 US patients and >100,000 cases worldwide. NMOSD disproportionately affects females (up to 7:1).[9,10] Positive anti–aquaporin-4 (AQP4) antibody neuromyelitis optica (NMO-IgG) is the most common disease serotype; however, titers fail to predict disease course.[11,12] Recent evidence[13,14] suggests that cases positive for anti–myelin oligodendrocyte glycoprotein (MOG) antibody (MOG-IgG) are pathogenically distinct from NMOSD.

Although studies suggest therapeutic benefit, no treatment of NMOSD has been found to be safe and effective in prospective, adequately powered clinical trials. However, recent results from phase IIb and phase III trials are encouraging.[15–17] In these trials, biologic therapeutics being evaluated include those targeting the complement C5 protein, the intereukin-6 receptor, and CD-19 protein on B cells. In addition, new and important scientific insights have recently shed light on key mechanisms underpinning NMOSD pathogenesis that may represent targets for next-generation therapeutics.[18–21]

By comparison, few studies have systematically examined the impact of NMOSD on quality of life (QoL) in well-characterized cohorts.[22–25] Therefore, The Guthy-Jackson Charitable Foundation, Alexion Pharmaceuticals, Chugai Pharmaceutical Co., MedImmune/Viela Bio, and Ipsos Public Affairs conducted a cooperative study of NMOSD patient experience and QoL. Through an interactive survey format, patient-reported clinical, demographic, and experiential data were systematically collected from geographically dispersed patients with NMOSD across North America. The current analyses yielded novel insights that may afford potentially modifiable aspects of personal or clinical care to improve QoL in patients with NMOSD.

Methods

Clinical research standards

Human subjects protection
The study was conducted in accordance with 45 Code of Federal Regulations Part 46 and the US Department of Health and Human Services policies regarding conductance of Human Subject Research. Protocols, survey instruments (figure e-1, links.lww.com/NXI/A120), and informed consent documents were approved by a central institutional review board. Written and verbal consent/assent were obtained before enrollment.

Special population compliance
The online survey instrument was compliant with the Americans with Disabilities Act. Participants were given the option of completing the survey with assistance of a relative, friend, or caregiver if physical impairments precluded independent participation.

Study goals and design

Study goals
Goals were (1) to gain understanding of the natural history of NMOSD from a patient-reported perspective and (2) to assess NMOSD patient QoL using a rigorous survey methodology comprising standardized and NMOSD-specific QoL measures. Both goals were intended to identify how NMOSD affects patients and in so doing identify those aspects that might be modified.

Study design
This study used a cross-sectional survey design. Comparative disease data were derived from published studies, which used identical standardized measures and for which parallel demographic and QoL data sets were available.

Survey themes
The survey instrument assessed multiple disease impacts using quantitative Likert scales with dynamic ranges respective of each theme:

Health-related QoL
Three validated scales were used to assess the impact of NMOSD on health-related QoL: (1) select items from the Role-Physical and Role-Emotional subscales of the Short Form-36 (SF-36) measured the impact of NMOSD on physical and emotional health.[26] Scores on the SF-36 subscales ranged from 0 to 100 (100 = highest functioning and 0 the lowest). The scale is normalized to average US individuals having a score of 50; (2) the MS QoL scale[27] measured effects of pain, bowel and bladder, and sexual function; (3) the Impact of Visual Impairment Scale assessed of visual impairment affected perceived QoL.[28]

Perceived impact of NMOSD on daily living
Parameters were measured by (1) overall QoL (distinct from health-related QoL); (2) perceived impact on career; (3) social life; (4) personal relationships; (5) reproduction choices; (6) NMOSD-related pregnancy complications; and (7) degree to which living situation was determined by necessity.

Diagnostic experience

Measures included date of initial diagnosis (month/year); presenting symptoms; and diagnostic history, including time between first symptoms, initial diagnosis, and NMOSD diagnosis.

Treatment experience

The following data were collected: treatment history; reason for treatment change; date of most recent treatment change; perceived effectiveness of current NMOSD treatment; concerns regarding current treatment; and outlook on future treatment.

Relapse experience

Relapses in the previous year were measured using several aspects of impact and severity, including total number and frequency of clinically-confirmed relapses; number requiring inpatient hospitalization; treatment regimens received for relapses; average duration of relapses; and frequency of emergency/urgent care for NMOSD.

Health care experience

Evolution of patient interactions with health care professionals was assessed by first presentation to a health care provider with symptoms consistent with NMOSD; initial referral to an NMOSD specialist; specialty of physician diagnosing NMOSD; factors influencing choice of current physician; frequency of scheduled clinical evaluations; and level of satisfaction with NMOSD physician/health care provider.

Economic burden

Specific financial impact of NMOSD was estimated via time spent traveling to/from medical appointments; method of transportation; need for in-home professional care; total costs and annual out-of-pocket expenses for care; financial support received; burden of monthly out-of-pocket expenses; and perceived sufficiency of health care insurance.

Future uncertainty

Future concerns of worsening of disease and unpredictable development of improved therapies were assessed.

Survey translation

Translation of the survey into Spanish involved a 2-step process. First, a native-speaking translation linguist reviewed documents against the source English file for consistency, terminology, and syntax. Next, a computer-aided translation tool (Translation Workspace XLiff Editor, v.2.49.1)[29] was applied to review the instrument in contextual modules, resolving semantic ambiguity.

Eligibility and enrollment

Eligibility

Participants were recruited from an opt-in digital mailing list of 2,000 individuals in the NMO advocacy community who requested information. Those fulfilling inclusion criteria were study eligible: self-reported, established diagnosis of NMO or NMOSD[30,31] and the ability to read textual content or hear questions audibly and respond to questions.

Enrollment and implementation

Eligible subjects were consented and enrolled. The survey instrument was implemented either by telephone or via an online interface. Both modalities offered assistance through a clinical study coordinator and provided options allowing completion in 1 session or to complete over multiple sessions. Patient-reported clinical data assessed are summarized in figure e-1 (links.lww.com/NXI/A120). Survey completion most commonly occurred in the patient or caregiver residence. Caregivers sometimes assisted the patient and investigator in use of the computer interface or in patient historical recall.

Informatics and data security

Study data were collected using a web-accessible electronic data capture system with access limited to qualified study personnel. Each patient data set was curated for quality, internal consistency, and completeness.

Statistical analyses

Descriptive statistics (medians or interquartile ranges for numeric variables; counts or percentages for categorical variables) were evaluated to assess cohort demographic diversity. Pairwise analysis of variance (ANOVA), χ^2 tests, and Pearson or Spearman correlation analyses were used to assess magnitude and orientation of relationships between or among study variables. All analyses were performed in SPSS v. 25.0.[32] Probability values (p) <0.05 and correlation values (r) > or < 0.5 were considered significant.

Data availability

Deidentified data obtained using the survey instrument used in the current study (figure-e1, links.lww.com/NXI/A120) will be made available to qualified research personnel in accordance with institutional review board policies and upon request approximately 6 months following the final publication date.

Results

Cohort demographics

Sex, race, and ethnicity

The study population was predominantly female (N = 171; 88.6%) and comprised diverse racial/ethnic backgrounds: 71.5% Caucasian/white; 16.1% African American/black; 6.7% Asian (AS); 6.7% Hispanic/Latina/o or Spanish American; 0.5% Native American, 1.0% Pacific Islander; and 2.6% Other. The distribution exceeds 100% because individuals could select multiple categories. The sample was predominantly English speaking; 2 participants requested the Spanish survey. Race and ethnicity distribution was generally representative of the U.S. population, but reflected a smaller proportion of HL participants than expected.

Education

Twenty-eight percent reported completing a primary or high school education or general educational development (figure 1A). Twenty-one percent hold an associates or technical

A.
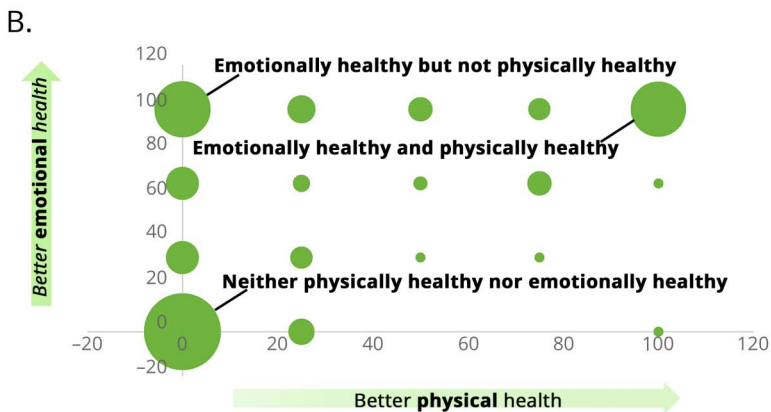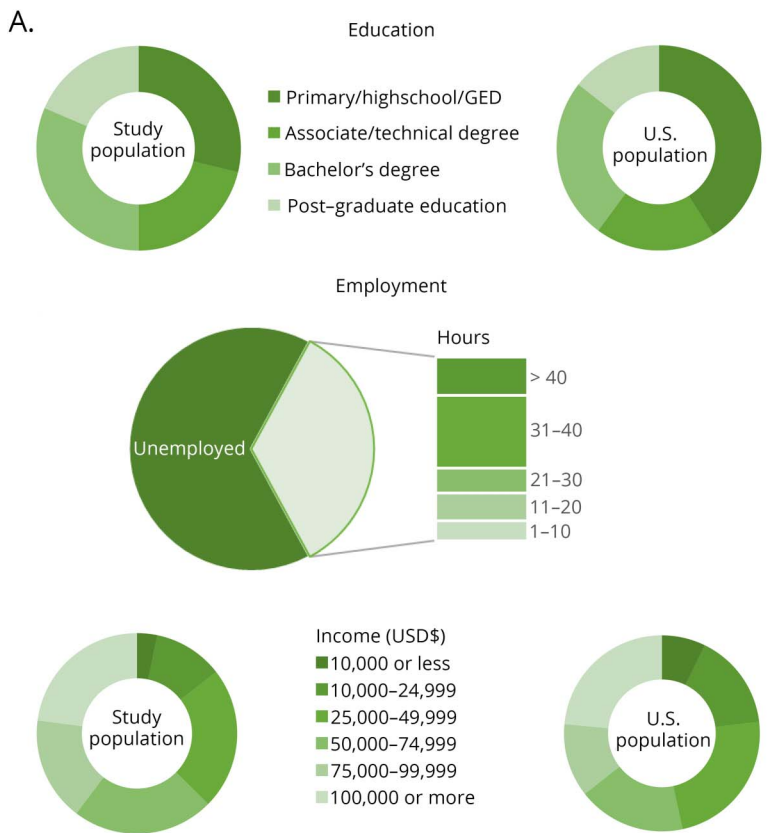
(B) Relationship between physical and emotional health functioning in NMO/SD. Criteria were based on SF-36 role-physical and role-emotional health measures. The relative size of the circle represents the number of respondents with a given score. Most respondents fell within one of 3 categories, as labeled. Note that the upper left category represents a particularly resilient group of patients with very poor physical health but very robust emotional health.

degree, 30.6% hold a bachelor's degree, and 18.1% have a postgraduate education or professional degree. Typical of online survey research, the sample skewed slightly to a greater proportion of subjects having a higher level of education than the general US population.

Employment status

Approximately 35% of the study cohort (N = 67) reported current employment (figure 1A), ranging from full-time (≥40 h/wk; 21.2%) to part-time work. Nine unemployed respondents (4.6%) reported that they are actively seeking employment. Of those unemployed, 18 are full-time homemakers or caregivers, 22 are retired, and 1 is a student. Most unemployed respondents (63.7%; N = 79) reported being disabled.

Income

Household annual income varied widely among the study subjects (figure 1A). The study population comprised a smaller proportion of participants who earned less than $10,000 per year compared with the broader US demographic.

Residential status and children

Study participants resided in one of 43 US states and the District of Columbia, whereas 11 participants resided in Canada. The modal state of residence was California (N = 27; 14.8%). The majority of participants (70.5%) lived with their spouse/partner; 38.3% with their children; 10.4% were living alone at the time of study. None reported living with domestic assistance or in an

institutional domicile/care facility. Most participants (73.1%) had children.

Survey assistance and future research

Nineteen participants (<10%) received assistance in survey completion. One participant participated by telephone. Over 92% of study subjects (N = 179) would consider participating in a future study, whereas 8 (4.1%) declined considering a future survey and 6 (3.1%) declined to answer this question.

Overall QoL

Physical and emotional health

Role-physical scores were relatively low but exhibited wide variability (median = 27.1 ± 36.1). Role-emotional functioning was near-average, with broad variance (median = 54.0 ± 44.9). Data exhibited bimodal distribution, with participants chiefly reporting either low or high functioning (figure 1B). Although physical and emotional health were positively correlated ($r = 0.513$; $p < 0.05$), the data also highlighted a complex health continuum (figure 1B).

Comparative QoL

To contextualize NMOSD QoL, SF-26 data were compared with data examining other autoimmune/inflammatory disorders (table 1). Where results are summarized physically, NMOSD impact on QoL was rated similarly to systemic lupus erythematosus. Emotional impact of NMOSD was rated as

Table 1 Comparative impact and determinants of NMO/SD impact on QoL

Comparative Disease cohort	Sample size	Physical[a]		Emotional[a]		Source
		M	SD	M	SD	
Current study	193	27.1	39.1	54.0	44.9	—
Other NMO[b]	30	36.0	10.7	46.7	10.9	Zhao et al.[14]
MS[c]	368	18.0	NA	52.0	NA	Riazi et al.[35]
Parkinson disease[c]	227	19.0	NA	34.0	NA	Riazi et al.[35]
Systemic lupus erythematosus	1,316	36.3	41.5	54.5	43.9	Wolfe et al.[36]
Amyotrophic lateral sclerosis	679	18.2	33.1	47.3	46.2	Jenkinson et al.[37]
Rheumatoid arthritis	13,722	39.9	42.0	63.5	42.4	Wolfe et al.[36]
NI rheumatic disorders	3,623	39.5	41.6	65.6	41.4	Wolfe et al.[36]
Antiphospholipid syndrome	270	43.5	49.6	56.8	49.4	Georgopoulou et al.[33]
Fibromyalgia	2,733	19.2	32.3	43.9	43.9	Wolfe et al.[36]
Determinant		Range		Mean		SD
Overall QoL		1–6		4.58		1.41
Bodily pain		1–6		3.60		1.31
Impaired career		1–6		3.30		1.96
Ability to work at job		1–6		3.19		1.96
Affected choice whether to have children		1–6		2.11		1.88
NMO/SD-specific issue						
Bowel/bladder function interfering with normal activities		1–5		2.26		1.28
Interfered with day-to-day work (inside or outside the home)		1–5		2.76		1.25
Satisfaction with sexual function		1–5		2.40		1.23
Social and personal relationships						
Social life		1–10		5.40		3.05
Personal and family relationships		1–10		5.66		2.80

Abbreviations: MCS = Mental Health Component; NA = not available; NI = non-inflammatory; NMO = neuromyelitis optica; PCS = Physical Component Summary; QoL = quality of life; SF = Short Form.
[a] SF-36 scores on role-physical (physical functioning) and role-emotional (emotional functioning) of respondents diagnosed with NMO or NMOSD vs other comparison conditions of similar heterogeneity.
[b] Zhao et al report the SF-36 PCS score and MCS Summary Scale, a broader scale, which contains the role-physical and role-emotional subscales but captures a broader range of physical and mental/emotional functioning.
[c] Riazi et al. did not report SDs for subscale means.

equivalent to MS, systemic lupus erythematosus, and anti-phospholipid syndrome.

NMOSD-specific experience

Impact of disease on QoL
Specific impacts of NMOSD on QoL are summarized in table 1. On average, NMOSD imposed a significant negative effect (mean = 4.58 ± 1.41; scale 1–6 [1 = least impact, 6 = greatest impact]); >70% reported QoL to be greatly affected. Determinants most associated with negative QoL were pain, impact on career, and ability to work. Other factors were pain impairing day-to-day tasks, impact on social activities, bowel/bladder dysfunction, and satisfaction with sexual function. Of interest, diagnosis of NMOSD failed to strongly influence the decision to have children.

Initial presenting Symptom(s)
The most common initial presenting symptoms (table 2) were numbness and/or tingling (68.4%), difficulty walking (54.4%), and visual disturbances (52.8%). Other presenting symptoms are as in figure-e1 (links.lww.com/NXI/A120).

Accuracy of initial diagnosis
Nearly two-thirds of the cohort (N = 125; 64.8%) reported an initial diagnosis other than NMOSD. The most frequent were MS (N = 80; 41.4%) or nonspecific optic neuritis (N = 44; 22.7%) (table 2).

Demographics and serologic status
Participants ranged in age from 19 to 76 years (mean = 49.2 ± 12.8 years), whereas 13–73 years (mean = 44.7 ± 12.5 years) at diagnosis and 3 months to 22 years (mean = 5.0 ± 3.8 years) from diagnosis to study enrollment. Eighty-two percent carry the diagnosis of NMO (N = 158), whereas 18.1% (N = 35) were diagnosed with NMOSD. Among the entire study cohort, 118 (61.1%) reported being anti–aquaporin 4 antibody (NMO-IgG) seropositive, 41 (21.2%) NMO-IgG seronegative, and 34 (17.6%) did not know.

Diagnostic or treatment delays
Time from initial symptoms to correct diagnosis ranged from 0 (i.e., immediate NMO diagnosis) to 40 years (mean = 3.3 ± 6.3 years). The time from correct diagnosis to treatment initiation ranged from 0 to 11 years (mean = 6 months ± 1.7 years). The median timespan between first symptom and correct diagnosis was 6 months, and the median interval to specific treatment initiation was 3 weeks.

Perceived efficacy of current treatment
The mean rating of perceived effectiveness of current treatment across all participants was 8.2 ± 2.3 on the following scale (1–10): 10 = treatment works very well; 1 = treatment does not work well or at all. The most common medications were rituximab (60.6%), prednisone/corticosteroids (20.2%), and mycophenolate mofetil (17.1%). Of treatments being prescribed for at least 10% of study subjects, those receiving

Table 2 Symptoms and diagnoses of initial disease episode among patients with NMO/SD

	Count[a]	Percent[a]
Initial symptoms		
Numbness/tingling	132	68.4
Difficulty walking	105	54.4
Vision problems	102	52.8
Pain	95	49.2
Fatigue	66	34.2
Bladder control problems	51	26.4
Paralysis	45	23.3
Spasticity (sudden involuntary contraction of a muscle)	45	23.3
Bowel control problems	30	15.5
Protracted vomiting	25	13.0
Cognitive problems (such as memory, mood, and mental effectiveness)	27	14.0
Protracted hiccups	21	10.9
Excessive daytime sleepiness	22	11.4
Depression	20	10.4
Insomnia	17	8.8
Emotional symptoms	14	7.3
Sexual dysfunction	10	5.2
Initial diagnoses		
MS	80	64.0
Optic neuritis	44	35.2
Transverse myelitis	37	29.6
Depression	12	9.6
Lupus	9	7.2
Stroke	5	4.0

Abbreviation: NMO = neuromyelitis optica.
[a] Patient may have reported more than 1 diagnosis before NMO/SD.

rituximab or mycophenolate mofetil reported highest perceived efficacy, whereas azathioprine was lowest (table 3). Four participants reported currently receiving no treatment, and 35 (18.1%) reported "other" treatments.

Concerns about treatment options
More than 50% of participants (51.8%) reported having concerns regarding their NMOSD treatment, mostly focused on future effectiveness (table 3). Eighty-eight participants (45.6%) reported NMO medication changes over their disease course. The majority of these patients (N = 48, 54.5%) reported changes because of poor efficacy, whereas 32

Table 3 Perceived effectiveness, concerns, and history of treatment among patients with NMO/SD

Current treatment	Count	Percent	Rating of current treatment	SD	Range
Rituximab	117	60.6	8.76	1.88	1–10
Prednisone/corticosteroid	39	20.2	7.69	2.53	2–10
Mycophenolate mofetil	33	17.1	8.30	2.11	2–10
Azathioprine (Imuran)	28	14.5	7.39	2.36	2–10
PLEX	12	6.2	9.00	1.48	5–10
Investigational drug/clinical trial	3	1.6	10.00	—	—
Cyclophosphamide	1	0.5	8.00	—	—
Tocilizumab	1	0.5	10.00	—	—

	Count	Percent
Treatment concern		
Future treatment effectiveness	56	56.0
Side effects	46	46.0
Ongoing significant disability	23	23.0
Ongoing relapses	19	19.0
Discomfort during administration	13	13.0
Inconvenience	11	11.0
Impact on pregnancy decisions	7	7.0
Treatment history		
Azathioprine	47	53.4
Prednisone/corticosteroid	47	53.4
Mycophenolate mofetil	30	15.5
Rituximab	21	23.9
PLEX	16	18.2
IVIG	6	8.8
Cyclophosphamide	5	5.7
Investigational drug/clinical trial	4	4.5

Abbreviations: IVIG = intravenous immunoglobulin; NMO = neuromyelitis optica; PLEX = plasma exchange.
Participants could be taking more than 1 medication; rating of current treatment captures the specific medication listed in the table and any other medications or treatments they were currently undergoing.

(36.4%) reported intolerable side effects. Three patients (3.4%) changed medication during pregnancy, 4 (4.5%) participated in a clinical trial, and 10 (11.4%) changed therapy because of cost (table 3).

Impact of relapses

Table 4 summarizes relapse frequency among study participants. Fifty-two patients (26.9%) reported no relapses. Among the remaining 141 patients, 115 (81.5%) reported relapses requiring hospitalization, whereas 26 (18.5%) had relapses managed as outpatients. Forty-five participants (23.3%) reported 6 or more relapses, with 2 patients having

≥6 in the previous year. One-hundred twenty-one patients had not visited an emergency department because of relapse in the past year, whereas 6 others visited an emergency department ≥6 times. Relapses were reported as lasting <4 weeks by 95 participants (49.2%) (table 4); 8 patients (4.1%) reported relapses lasting >6 months. Most participants who experienced relapses in the past year were treated with either IV or (44%) or oral steroids (44%).

Health care experience

The distribution of health care professionals initially sought by patients for care is summarized in table 5. Primary care

Table 4 Total and annual relapse profile of study participants

Relapse frequency	0	1	2	3–5	6+
Relapses ever experienced					
Relapses experienced	52	33	22	38	45
Relapses requiring hospitalization	26	40	18	35	18
Relapses in the previous year					
Relapses experienced	85	34	7	9	2
Relapses requiring hospitalization	23	17	6	6	0
No. of emergency department visits	121	30	18	18	6

Relapse duration	Count	Percent
1–7 d	30	22.7
1–2 wk	37	28.0
2–4 wk	28	21.2
1–2 mo	12	9.1
3–4 mo	11	8.3
5–6 mo	6	4.5
More than 6 mo	8	6.1

physicians (N = 48; 24.9%) and general neurologists (N = 47; 24.5) were most commonly consulted initially, followed by emergency department physicians (N = 41; 21.2%). The most common initial referral was to a general neurologist (N = 77; 39.8%). Fifty-two patients (26.9%) were referred to NMOSD specialist neurologists, 40 (20.7%) to an ophthalmologist, and 26 (13.4%) to a gastroenterologist. General neurologists were the most common specialists prescribing medications (~90.6%).

Nearly one-half of the study cohort (N = 82; 42.4%) were examined by their doctor every 6 months, most commonly coincident with rituximab infusion. Thirty-three percent (N = 64) of patients saw their doctor at 3-month intervals; 16 (8.3%) once per year, 2.6% (N = 5) every month, and 6 (3.1%) only at the time of relapse. The remainder report seeing their doctor "as needed" (N = 4) or not at all (N = 1).

Economic burden of disease

Costs attributable to disease
Study participants rated monthly out-of-pocket expenses due to NMOSD as 5.71 ± 3.12 on a 10-point scale ranging from no burden (1) to significant burden (10). As summarized in table 5, prescription medicines accounted for the greatest portion of NMOSD medical costs for most patients (N = 88; 45.6%); many specified rituximab infusions as the single largest cost. The sole factor predictive of financial burden was receiving plasma exchange therapy during relapse. Twenty-five (13%) reported travel costs to/from health care providers as accounting for the greatest cost, whereas 18 (9%) stated

hospitalization accounted for greatest cost. Eleven percent (N = 21) reported that an in-home professional caregiver provides service. Other significant costs reported were herbal supplements, psychologist visits, or medical costs not covered by Medicare.

Total costs
Beyond subjective financial burden of disease, the total annual expenses reported by the cohort as a whole was $1,109,357 or an average of $5,748 per respondent (table 5). The most frequently reported cost was prescription medication, with 140 participants (73.5%) reporting an average out-of-pocket cost of $1,876 annually. Unprompted (not an original category of out-of-pocket costs), 3 participants reported lost income at an average of $65,000 annually. Although not a categorical option, 23 respondents reported paying for specialists (including psychologists) out-of-pocket, at an average of $1,554 annually. A large number of participants (N = 124; 64.2%) reported travel costs to medical appointments, at an average of $468 per respondent. The largest total cost out-of-pocket was for hospitalization, accounting for $304,410 annually in the sample, or an average of $7,248 per respondent (N = 42; 21.8%). Caregiver or support was another high cost, accounting for $70,580 annually in the sample, or an average of $3,361 per respondent (N = 21; 10.9%).

Financial support for care
The majority of study participants (N = 142; 73.6%) reported that health insurance sufficiently covered prescribed NMOSD medicines. Among those with insufficient health insurance, expensive copayment and insurer denials were common

Table 5 Health care professionals encountered and annual expenses due to NMO/SD

Health care professional	Physician first to evaluate symptoms	Specialist first to receive referral	Physician who diagnosed NMO/SD	Physician currently prescribing medications
Neurologist (nonspecialist)	47	77	99	175
Neurologist (NMO specialist)	24	52	83	—
Ophthalmologist	21	40	11	0
Neuro-ophthalmologist	1	3	3	0
Rheumatologist	4	5	0	1
Gastroenterologist	1	26	16	0
Orthopedist	1	3	0	0
MS specialist	0	4	4	5
Primary care physician	48	1	0	11
Emergency department physician	41	1	1	0
Hematologist	0	1	0	13
Physiatrist	0	0	0	1
Other	5	8	5	4

Out-of-pock expenses	N	Minimum	Maximum	Median
Prescription medicine(s)	140	$25	$30,000	$540
Travel to clinical care	124	$10	$10,000	$115
Emergency/urgent care	48	$50	$15,000	$275
Medical supplies	52	$50	$3,000	$330
Hospitalization	42	$100	$150,000	$1,950
Caregiver or service	21	$50	$14,000	$1,500
Support groups	7	$8	$360	$100
Other costs	58	$80	$125,000	$1700

Category of expense[a]	Total cost to sample respondents	No. of respondents reporting cost	Average annual cost per respondent
Prescription medicine(s) (including infusions)	$262,598	140	$1,876
Emergency/urgent care	$61,275	48	$1,277
Hospitalization	$304,410	42	$7,248
Travel costs for medical care	$58,003	124	$468
Caregiver or support services	$70,580	21	$3,361
Medical supplies	$34,173	52	$657
Support group	$1,838	7	$263
Supplements	$1,000	1	$1,000
Specialists	$35,750	23	$1,554
Lost income	$195,000	3	$65,000
Health insurance deductible	$23,330	9	$2,592
Other costs (unspecified)	$61,400	4	$15,350

Continued

Table 5 Health care professionals encountered and annual expenses due to NMO/SD *(continued)*

Category of expense[a]	Total cost to sample respondents	No. of respondents reporting cost	Average annual cost per respondent
Collective sample	$1,109,357	193	$5,748

Abbreviations: NMO = neuromyelitis optica; QoL = quality of life.
[a] For each cost category, respondents rated the largest burden on QoL and estimated annual expense for each. Costs were totaled by category and averaged for cost-per-respondent and cost-in-sample estimates. Note: Other costs category included specialists, estimated lost income, health insurance deductibles, and unspecified costs.

reasons. Twenty-four study participants (12.6%) reported receiving financial support for their NMOSD treatment, largely in the form of disability insurance, clinical trial participation, or support from friends and family.

Correlation analysis

To examine predictors of overall QoL, ANOVA was used to detect correlates among individual factors, including time since diagnosis, total relapse number (a surrogate of disease severity), and current treatments (overall and specifically for relapses). Neither time since diagnosis nor current treatment regimen was predictive of overall QoL; however, the number of relapses correlated significantly with overall QoL ($p = 0.001$), with greater numbers of relapses diminishing QoL.

Other potential correlates affecting QoL in NMOSD were explored using a matrix Pearson or Spearman correlation analysis of primary data elements. As shown in table 6, multiple correlations were identified as trending to positively or negatively affecting QoL.

Discussion

The primary goal of this study was to determine the impact and correlates of NMO on patient QoL in a standardized manner using validated measures of physical and emotional health impact on daily activities potentially affecting QoL. By examining specific tangible domains of QoL in parallel to perceived overall QoL, the patient experience regarding how this rare disease affects daily life was revealed.

Several important themes were identified among the current study cohort. First, NMOSD typically has strong negative effects on physical functioning. Physical functioning was

Table 6 Exploratory correlation analyses among study data elements†

Data Element	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
1. Age	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
2. Serostatus = Seropositive	.308	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
3. Serostatus = Seronegative	-.261	-.651	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
4. Serostatus = Unknown	-.113	-.580	-.240	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
5. Physical Health Functioning	-.186	-.088	-.017	.131	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
6. Emotional Health Functioning	-.022	-.017	-.039	-.064	.453	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
7. QOL: Overall Quality of Life	.221	.134	-.102	-.063	-.482	-.355	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
8. QOL: Affect ability to work	.075	.005	.129	-.134	-.675	-.444	.543	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
9. QOL: Bodily pain	.214	.018	-.046	.026	-.501	-.423	.605	.487	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
10. QOL: Bowel & Bladder	.209	.018	.040	.040	-.337	-.194	.407	.279	.335	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
11. QOL: Sexual Function	-.118	-.018	.045	-.024	.143	.358	-.320	-.194	-.215	-.203	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
12. QOL: Children	-.515	-.114	.159	-.023	.160	-.064	-.120	.048	-.117	-.161	.047	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
13. Social and Family Life	.042	.069	-.029	-.056	-.170	-.247	.204	.436	.193	.180	-.191	-.023	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
14. Future Uncertainty	.212	.043	.041	-.100	-.248	-.105	.277	.371	.158	.136	-.192	-.054	.064	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
15. Symptom: Spinal	.044	.035	-.050	.057	-.051	.070	-.002	.144	.177	.212	.002	-.005	.128	-.079	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
16. Symptom: Optic	.029	.035	.085	-.135	-.005	.074	.086	-.189	.029	-.011	-.113	-.047	.023	-.026	-.365	--	--	--	--	--	--	--	--	--	--	--	--	--	--
17. Symptom: Nonspecific	-.509	.188	-.063	-.173	-.070	-.174	-.041	.136	.138	.060	-.060	.090	.077	-.032	.408	-.143	--	--	--	--	--	--	--	--	--	--	--	--	--
18. Symptom: Area Postrema	-.163	.117	-.106	-.036	-.016	-.040	.099	-.047	-.057	.020	-.026	.142	.033	-.065	.119	.153	.069	--	--	--	--	--	--	--	--	--	--	--	--
19. Symptom: Cerebral	.021	.046	-.027	-.030	-.152	.193	.138	.007	.228	.165	-.066	.011	.130	-.008	.231	.271	.173	--	--	--	--	--	--	--	--	--	--	--	--
20. Symptom: Other	-.016	-.033	.067	-.029	-.153	-.004	.007	.112	-.039	.031	-.121	-.083	.017	-.175	.050	.178	.050	-.064	--	--	--	--	--	--	--	--	--	--	--
21. Tx: NS Non-medicinal	.033	.129	-.038	-.124	-.099	-.131	.060	-.006	.127	-.045	-.123	.222	.032	-.001	.097	-.036	.137	.007	-.049	-.122	--	--	--	--	--	--	--	--	--
22. Tx: NS Immune-suppressing	.050	.035	-.047	.006	-.056	-.072	.127	.148	.058	-.004	.013	-.034	-.081	-.039	-.096	.138	-.086	-.035	.038	-.038	-.027	--	--	--	--	--	--	--	--
23. Tx: Specific Immune-Suppressing	-.106	-.148	.149	.029	-.019	.015	.008	-.024	-.032	.039	-.025	.019	-.007	-.050	.079	-.126	.045	.083	-.051	.047	.084	-.533	--	--	--	--	--	--	--
24. Tx: NS Immune-neutralizing	.006	-.023	.072	-.047	-.014	-.010	.029	.001	.008	.044	-.033	-.066	-.085	-.020	.006	-.020	-.042	-.041	-.046	.177	.013	-.025	--	--	--	--	--	--	--
25. Tx: Other	.058	.034	-.094	.057	-.019	-.086	.033	-.062	.056	-.070	-.011	-.074	-.041	.027	.034	-.053	.047	.010	-.028	.103	.015	.174	-.188	.109	--	--	--	--	--
26. Tx: None	.068	-.101	.083	.040	.008	-.021	-.038	-.074	.054	.062	.003	.018	.104	.043	-.011	-.012	-.041	-.086	.141	.044	-.056	-.183	-.264	-.021	-.082	--	--	--	--
27. Polypharmacy	.005	-.068	.089	-.009	-.084	-.056	.136	.091	.135	-.031	-.021	.026	-.010	.029	-.008	.028	.049	.006	.015	-.033	.377	.427	.174	.180	-.519	-.118	--	--	--
28. Treatment Rating	-.022	.038	.086	-.040	.162	.215	-.314	-.145	-.269	-.201	.122	.009	-.033	-.103	-.109	-.012	-.012	.139	-.093	.041	-.199	.303	.107	-.128	-.142	-.004	--	--	--
29. Concern About Treatment	.052	.038	.001	-.049	-.162	-.064	.092	.029	.008	.067	-.054	.061	.057	.230	-.074	.035	.103	.069	.104	-.063	.050	-.010	-.060	.098	.042	.019	.022	-.315	--
30. Financial Burden	-.046	-.175	.182	.027	-.229	-.216	.216	.147	.287	.171	-.053	-.016	.075	.218	.013	.025	.038	-.151	.160	.075	.088	-.049	.080	.127	-.064	-.038	.075	-.067	.082

† Pearson Correlations were performed for [binary x binary] correlations or [continuous x continuous] correlations; Spearman Correlations were performed for [binary x continuous] correlations. Bold values represent *r* values that are statistically significant at the 95% level (*p* < .05). QOL = Quality of Life; Tx = Treatment; NS = non-specific. Positive correlations (r values) are green cells ranging from weak (mint) to strong (forest); negative correlations (r values) are red cells ranging from weak (pink) to strong (red).

lower in the study cohort than in the general population and on par with individuals having MS or systemic lupus erythematosus.[33–36] The predominant physical issues affecting QoL were bodily pain, bowel and bladder dysfunction, and visual impairment. These factors inversely correlated with ability to work, the limitation of which negatively affected QoL. Age was positively associated with many QoL measures such as pain, suggesting that disease increasingly negatively affctes QoL over time. Worse physical functioning also correlated with greater uncertainty about the future. Notably, anti-AQP4 antibody serostatus reported as negative or unknown correlated with less impact on QoL than detectable anti-AQP4 antibody. This relationship is similar to that often observed in AQP4 antibody–positive and MOG antibody–positive phenotypes.[11–14] Conversely, seronegative status carried a significantly higher financial burden.

By comparison, emotional health was in general unimpaired, suggesting that poor physical health does not necessarily correspond to diminished emotional health. Although some study participants exhibited congruent emotional and physical health, a subset of participants reported the highest level of emotional health despite seriously impaired physical health. This inverse relationship suggests a degree of psychological resilience in some patients despite physical impairment. Likewise, a portion of participants reported that their disease had a positive effect on their social relationships. One possible explanation for such positive impact is that their disease provoked support network involvement. These findings are consistent with the concept and impact of psychological resilience,[38] which can translate to effective personal strategies of coping with health-related challenges.[39]

The constellation of presenting symptoms in many patients resulted in an initial diagnosis of MS. Inaccurate diagnosis combined with delay of appropriate therapy can negatively affect long-term outcomes in NMOSD.[40] However, recent implementation of international consensus criteria[31] has increased the timeliness and accuracy of diagnosis and should improve care in early disease.[41] The number, duration, and severity of relapses varied widely across the study cohort. This observation corresponds to the absence of a standardized definition and diagnostic algorithm for differentiating bona fide relapses from unrelated symptoms.

Not surprisingly, participants reporting higher treatment ratings also experienced higher physical and emotional functioning and higher QoL. Similarly, worse functioning was associated with larger financial burden. These themes are concordant with those of previous studies.[22,23,41] Of interest, patients receiving nonspecific immune-suppressing treatments tended to rate their regimens more negatively, whereas those on target-specific treatments (e.g., biologics) rated their treatments more positively. Impact of NMO on QoL extended beyond physical and emotional costs; respondents reported a high financial burden, particularly for prescription medicines, travel costs, hospitalization, and specialist care. Furthermore, the per-respondent cost and total cost estimates in this study provide a useful estimate of personal and health care costs of NMOSD to society.

Results of the current study emphasize the significant negative impact NMOSD can have on patient QoL, particularly in relation to physical disability, pain, bowel and bladder dysfunction, or visual impairment.[42–46] These manifestations correspond to reduced ability to work at a job or perform daily activities, and a decreased QoL, which also reconcile with negative impacts of anxiety, disability, or depression in NMOSD.[25,47] Factors contributing to these adverse outcomes may include (1) delayed or inappropriate treatment due to initial misdiagnosis; (2) real or perceived efficacy or lack of efficacy of current treatment options; (3) lack of a standard definition of relapse; and (4) disease-specific economic burden. These issues underscore the importance of recent advances in diagnostic timeliness and accuracy, as well as ongoing clinical trials intended to establish the first approved therapies for NMOSD. Prospectively, global collaboration aimed at implementation of a standard relapse definition and severity score should contribute to improved clinical care. Likewise, the pursuit of predictive biomarkers of relapse to allow mitigating interventions and the initiation of studies aimed to durably restore immune tolerance as a curative therapy hold promise for increasingly effective medical solutions for NMOSD patients. Synergistic and prospective approaches such as these aimed at addressing disease causes and effects hold great promise to significantly add to the QoL for patients with NMOSD, other patients with rare disease, and beyond.[48,49]

Disclosure

J. Beekman is an employee of Ipsos Public Affairs, a research firm paid to conduct this research study. A. Keisler was an employee of Ipsos Public Affairs, a research firm paid to conduct this research study. O. Pedraza is an employee of Ipsos Public Affairs, a research firm paid to conduct this research study. M. Haramura is an employee of Chugai Pharmaceutical Co., Ltd., which is conducting clinical trials focused on NMOSD and a sponsor of the current study.

Publication history

Appendix Authors

Name	Location	Role	Contributions	Disclosure(s)
Jennine Beekman, PhD	Ipsos Public Affairs, Washington, DC	Author	Designed/conceptualized the study; acquired the data; analyzed the data; interpreted the data; and drafted the manuscript for intellectual content.	Dr. Beekman is an employee of Ipsos Public Affairs, a research firm paid to participate in this research study.
Aysha Keisler, PhD	Ipsos Public Affairs, Washington, DC	Author	Designed/conceptualized the study; acquired the data; analyzed the data; interpreted the data; and drafted the manuscript for intellectual content.	Dr. Keisler was an employee of Ipsos Public Affairs, a research firm paid to participate in this research study.
Omar Pedraza, MPH	Ipsos Public Affairs, Washington, DC	Author	Designed/conceptualized the study; acquired the data; analyzed the data; interpreted the data; and drafted the manuscript for intellectual content.	Dr. Pedraza is an employee of Ipsos Public Affairs, a research firm paid to participate in this research study.
Masayuki Haramura, PhD	Chugai Pharmaceutical Co., Ltd.	Author	Designed/conceptualized the study; interpreted the data; and reviewed and revised the manuscript for intellectual content.	Dr. Haramura is an employee of Chugai Pharmaceutical Co., Ltd., which is conducting clinical trials focused on NMOSD.
Athos Gianella-Borradori, MD	Chugai Pharma USA, Inc.	Author	Designed/conceptualized the study; interpreted the data; and reviewed and revised the manuscript for intellectual content.	Dr. Gianella-Borradori was an employee of Chugai Pharmaceutical Co., Ltd., which is conducting clinical trials focused on NMOSD and a sponsor of this study.

Appendix *(continued)*

Name	Location	Role	Contributions	Disclosure(s)
Eliezer Katz, MD	Viela Bio	Author	Designed/conceptualized the study; interpreted the data; and reviewed and revised the manuscript for intellectual content.	Dr. Katz is an employee of Viela Bio, which is conducting a clinical trial focused on NMOSD and a sponsor of this study.
John N. Ratchford, MD	Viela Bio	Author	Designed/conceptualized the study; interpreted the data; and reviewed and revised the manuscript for intellectual content.	Dr. Ratchford is an employee of Viela Bio, which is conducting a clinical trial focused on NMOSD and a sponsor of this study.
Gerard Barron, BSc (Hons)	Viela Bio	Author	Designed/conceptualized the study; interpreted the data; and reviewed and revised the manuscript for intellectual content.	Mr. Barron is an employee of MedImmune, which is conducting a clinical trial focused on NMOSD and a sponsor of this study.
Lawrence J. Cook, PhD, MStat	University of Utah, Salt Lake City, UT	Author	Designed/conceptualized the study; acquired the data; analyzed the data; interpreted the data; and reviewed/revised the manuscript for intellectual content.	Dr. Cook is supported in-part by The Guthy-Jackson Charitable Foundation, which is a sponsor of this research.
Jacinta M. Behne, MS	Guthy-Jackson Charitable Foundation, Beverly Hills, CA	Author	Designed/conceptualized the study; interpreted the data; and revised the manuscript for intellectual content.	Ms. Behne is supported in-part by The Guthy-Jackson Charitable Foundation, which is a sponsor of this research.
Terrence F. Blaschke, MD	Stanford University, Palo Alto, CA	Author	Designed/conceptualized the study; interpreted the data; and revised the manuscript for intellectual content.	Dr. Blaschke is an Advisor to The Guthy-Jackson Charitable Foundation, which is a sponsor of this research.
Terry J. Smith, MD	University of Michigan, Ann Arbor, MI	Author	Designed/conceptualized the study; analyzed the data; interpreted the data; and drafted the manuscript for intellectual content.	Dr. Smith is an Advisor to The Guthy-Jackson Charitable Foundation, which is a sponsor of this research.
Michael R. Yeaman, PhD	University of California, los Angeles, CA	Author	Designed/conceptualized the study; analyzed the data; interpreted the data; and drafted the manuscript for intellectual content.	Dr. Yeaman is an Advisor to The Guthy-Jackson Charitable Foundation, which is a sponsor of this research.

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