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Costs and Health-Related Quality of Life in Patients With NMO Spectrum Disorders and MOG-Antibody–Associated Disease: CHANCE^{NMO} Study

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ABSTRACT

Objective

To evaluate costs and health-related quality of life (HRQoL) of neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein-antibody associated disease (MOGAD).

Methods

In this multicenter cross-sectional study, data on consumption of medical and non-medical resources and work ability were assessed via patient questionnaires. Costs were analyzed in EUR for 2018 from the societal perspective. HRQoL was captured by the EuroQoL EQ-5D-5L questionnaire. Clinical data were retrieved from the Neuromyelitis Optica Study Group (NEMOS) database.

Results

Two hundred twelve patients (80% women; median age 50 [19-83] years; median disease duration 7 [0-43] years; median Expanded Disability Status Scale [EDSS] 3.5 [0-8.5]; 66% Aquaporin-4 IgG, 22% MOG IgG positive, 12% double seronegative) were analyzed. The mean total annual per capita cost of illness accounted for EUR (Euro) 59 574 (95% CI 51 225 to 68 293; USD [United States dollars] 70 297, 95% CI 60 445 to 80 586), and the mean index value of the EQ-5D-5L was 0.693 (95% CI 0.65 to 0.73). The most important cost drivers were informal care costs (28% of total costs), indirect costs (23%) and drugs (16%), especially immunotherapeutics. Costs showed a positive correlation with disease severity ($\rho=0.56$, 95% CI 0.45 to 0.65); in the EDSS 6.5-8.5 subgroup the mean annual costs were EUR 129 687 (95% CI 101 946 to 160 336; USD 153 031, 95% CI 120 296 to 189 196). The HRQoL revealed a negative correlation to disease severity ($\rho=-0.69$, 95% CI -0.76 to -0.61); in the EDSS 6.5-8.5 subgroup the EQ-5D-5L mean index value was 0.195 (95% CI 0.13 to

0.28). Neither antibody status nor disease duration influenced the total annual costs or HRQoL.

Conclusion

These German data from the era without approved preventive immunotherapies show enormous effects of the diseases on costs and quality of life. An early and cost-effective therapy should be provided to prevent long-term disability and preserve quality of life.

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are rare but well characterized chronic autoimmune diseases of the central nervous system (CNS), mainly affecting the optic nerves and the spinal cord.^{1,2} Those affected can suffer severe physical disability even after the first attack.^{3,4} Recent data from smaller cohorts of 25 to 74 patients suggest a significant reduction in the quality of life of patients.⁵⁻⁸ However, exact data on the effects of NMOSD on patients' professional life, the need for long-term care and the total cost of illness (COI) are still missing. Until summer 2019, the disease was globally treated off-label with standard immunotherapeutics, preferably rituximab, azathioprine, or mycophenolate mofetil.^{4,9} New treatments have been and are still being implemented¹⁰, since four phase III trials indicate benefits for these new therapeutics of NMOSD.¹¹⁻¹⁴ Approval has already been granted in several countries for eculizumab, satralizumab, and inebilizumab. Given the extraordinarily high costs of the new drugs, a standardized and up-to-date analysis of the "pre-new therapy era" costs of this disease is overdue as guidance for physicians, health policy makers and healthcare providers. A recently published study reports on "patient experience and quality of life" in NMOSD.¹⁵ This study did not include patients with home care needs and therefore missed a socio-economically relevant part of NMOSD patients. Myelin oligodendrocyte glycoprotein-antibody associated disease (MOGAD) is an autoimmune disorder affecting the CNS in a partly similar clinical pattern as classical NMOSD but now considered a disease entity pathophysiologically distinct from NMOSD with Aquaporin-4 (AQP4) antibodies.¹⁶ There are no data on costs and health-related quality of life (HRQoL) for MOGAD to date. This underlines the need for independent research on disease costs and quality of life for these rare diseases. Accordingly, in September 2016 we initiated within the Neuromyelitis Optica Study Group (NEMOS) a Germany-wide study to assess the costs and health-related quality of life of patients with NMO spectrum disorders (CHANCE^{NMO}-Study). The primary

objective of this study was to assess the socio-economic impact of these diseases from the societal perspective together with the analysis of HRQoL and the main predictors thereof.

Patients and methods

Study design and study population

The study utilized a multicenter cross-sectional design and was conducted between 04/2017 and 04/2019 at 17 German NEMOS centers (www.nemos-net.de). Eligible patients were defined according to the following inclusion criteria: adult patients (≥ 18 years) with diagnoses of NMOSD according to International Panel for NMO Diagnosis (IPND) criteria 2015 and MOGAD who lived in Germany.^{1,17} Testing for serum antibodies for AQP4 and MOG immunoglobulin G (IgG) was performed by using an established cell-based assay.^{18,19} The majority of patients (42/46) with MOG-IgG were tested in at least two different cell-based assays.¹⁷ Exclusion criteria were predominant of the treatment for a disease other than NMOSD/MOGAD and severe cognitive impairment (informed consent not possible).

Standard protocol approvals, registrations, and patient consents

The study was approved by the ethics boards of the Hannover Medical School (no. 2016-7217) and other participating centers. All patients gave their written informed consent before enrollment.

Sample selection

Patients were examined for eligibility by an experienced clinician in the field of neuroimmunology during routine primary or follow-up NEMOS cohort visits. Of 275 available patients, 218 patients returned a complete questionnaire, and 212 datasets were available for analysis (Figure 1).

Outcome measures

Study participants were asked to answer a paper-based questionnaire (eQuestionnaire). Primary patient data on demographics, professional activity (and resulting impairment due to

the disease), and retrospective consumption of medical and non-medical resources were assessed.²⁰ Clinical data on disease onset, severity, duration, serostatus, symptoms, immunotherapy, and management of attacks were retrieved from the NEMOS database in which all centers prospectively update the information of every individual patient. Expanded Disability Status Scale (EDSS) was assessed by trained physicians during cohort visits. To investigate the patient self-reported HRQoL we applied the validated EuroQoL Group Five Dimension Five Level Scale (EQ-5D-5L).^{21,22}

Cost estimation

Cost estimation was performed from the societal perspective and by use of a micro-costing method following current recommendations for health economic evaluation.²³⁻²⁵ The utilization of medical and non-medical resources were assessed retrospectively within different recall periods to reduce recall bias (eTable 8). As we assumed a stable consumption of resources, we extrapolated costs to one year where appropriate. Costs were calculated in Euro (EUR) for the year 2018 (main recruitment period; 2018 average: EUR 1 = United States dollars [USD] 1.18). The main cost categories I. direct medical costs, II. direct non-medical costs, and III. indirect costs yield to the total COI. Direct costs consist of direct payments – from social and health insurance agencies or the patients themselves. Hereby, e. g., expenditures for drugs, medical consultations, or formal care are defined as direct medical costs, while travel expenses, investments in the home and car, and informal care result in direct non-medical costs. In contrast to formal care, non-trained personnel like relatives provide informal care. Lastly, indirect costs represent the loss of productivity of a patient and his or her caregivers due to absenteeism from work because of disability. A detailed explanation about cost valuation methods is provided in the Supplement.

Statistical analysis

The paper-based data were recorded in an Excel 365 (Microsoft) database by an independent double data entry for descriptive statistics. Statistical analysis was performed in SPSS

statistics version 26.0 (IBM) and Prism version 5.02 (GraphPad Software). D'Agostino-Pearson omnibus test was used to test for normal distribution of the data. Statistical significance of total COI, cost subcategories, and HRQoL parameters (index value, EQ-VAS, and EQ-5D-5L) between disease duration subgroups (0-1 vs. >5 and 0-5 vs. >5 years) was evaluated by nonparametric Mann-Whitney *U* test. In addition, the differences in resource utilization between mildly (EDSS 0-3) and severely (EDSS 6.5-8.5) affected patients were tested using this method. Multigroup comparisons were done with analysis of variance for nonparametric data (Kruskal-Wallis test with Dunn's multiple comparison test as a post-hoc test): The different serogroups (AQP4 IgG positive NMOSD, double seronegative NMOSD, MOGAD fulfilling and not fulfilling IPND criteria 2015) were analyzed for differences in total disease costs, cost subgroups, and HRQoL parameters (index value, EQ-VAS, and EQ-5D-5L). Likewise, subgroups of different disease severity (mildly affected [EDSS 0-3], moderately affected [EDSS 3.5-6], and severely affected [EDSS 6.5-8.5] patients) were examined for differences in resource utilization. To evaluate influencing factors on costs and HRQoL as dependent variables, we studied a variety of independent candidate variables. Due to the skewed nature of these dependent variables, we employed generalized linear models assuming the dependent variables follow a gamma distribution rather a normal distribution. We picked those independent variables that showed statistically significant results in univariate regression analysis and information at what point in the joint distribution the non-normality matters and analyzed them in two separated multiple linear regression models. In this context, the variables were assessed for collinearity and interaction. Data from multiple regressions were then entered into two generalised linear models with the appropriate link functions to generate the usability of the data regardless of their distribution. Due to this point and the right-skewness of our cost data, we calculated our 95% confidence intervals of the means with SPSS bootstrap function.^{26,27} Because of the explorative character of the study, we did not correct for multiple testing. Correlations between two non-parametric variables were

tested with Spearman's test (ρ). Data are expressed as mean and 95% confidence interval (95% CI). If not otherwise indicated, costs are presented in EUR (2018) per year. p -values <0.05 were considered as statistically significant. Missing data resulted in different numbers of patients analyzed.

This study was reported following the reporting guidelines to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).²⁸

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Characteristics of the study cohort

Two hundred twelve predominantly female ($n=170$, 80%) patients of mainly Caucasian descent ($n=199$, 94%) were enrolled in the study (Figure 1). Regarding the current diagnostic criteria, two thirds suffered from AQP4-antibody positive NMOSD ($n=141$, 66%) and about one in ten patients were diagnosed with double seronegative NMOSD ($n=25$, 12%).¹ All other patients ($n=46$, 22%) could be assigned to MOGAD, with 54% of these meeting the consensus criteria of the International Panel for NMO Diagnosis 2015.^{1,17} Social, educational and occupational information are given in more detail in eTable 1 in the Supplement. The number of study participants per federal state reflected the population distribution in German states (eTable 2 in the Supplement). In addition, this cohort is representative of the current NEMOS overall study population along relevant dimensions (e. g. regarding EDSS, age, and sex).

Direct medical costs

The mean direct medical costs per patient per year amounted to EUR 25 600 (95% CI 22 731 to 42 840; USD 30 208, 95% CI 26 823 to 50 551; Table 1). The most important cost driver

was medication including apheresis therapy (EUR 9 786, 95% CI 7 902 to 12 048 or USD 11 547, 95% CI 9 324 to 14 216; 38% of direct medical costs). Immunotherapies were used by 91% of all patients. Rituximab was the treatment of choice in the majority of all patients treated (68%, n=131). The distribution of immunotherapeutics within the patient cohort is shown in eTable 3. The other two most important cost drivers were inpatient hospital care costs (EUR 5 199, 95% CI 3 904 to 6 615 or USD 6 135, 95% CI 4 607 to 7 806; 20%), and costs for formal care (EUR 3 674, 95 % CI 1 807 to 6 393 or USD 4 335, 95% CI 2 132 to 7 544; 14%). Disease severity had an important impact on direct medical costs. This was particularly evident for formal care (Figure 2A and Table 1). For detailed characterization of resource utilization see supplemental eResults and eTable 4.

Direct non-medical costs

The mean direct non-medical costs were calculated at EUR 20 102 (95% CI 15 762 to 24 624, USD 23 720, 95% CI 18 599 to 29 056) per patient per year (Table 1). The main cost contributor was informal care (EUR 16 460, 95% CI 13 238 to 19 875 or USD 19 423, 95% CI 15 621 to 23 453; 82% of direct non-medical costs). Again, disease severity was a pivotal factor for the need of individual care. In total, 52% (n=111) of patients required informal care. The mean hours per day for informal care added up to 1.8 (95% CI 1.4 to 2.2, eTable 4). Accordingly, the reduction of working time by caregivers showed a correlation with increasing EDSS ($\rho=0.26$, 95% CI 0.12 to 0.39): from 0.3 (95% CI 0.0 to 0.81) hours per week in the mildly affected group (EDSS 0-3) to 4.4 (95% CI 1.5 to 7.8) in the severely affected group (EDSS > 6). Investments in home and car were made by 21% (n=45): 5% (n=5) in the mildly affected group and by 52% (n=17) of the severely affected patients. Around 75% of these costs had to be financed by the patients themselves (eTable 5).

Indirect costs

The mean indirect costs amounted to EUR 13 872 (95% CI 10 650 to 17 233; USD 16 369, 95% CI 12 567 to 20 335) per patient per year (Table 1). The two most important cost drivers

were loss of salary as an indicator for productivity loss due to days of sick leave (EUR 5 147 [95% CI 3 029 to 7 630] or USD 6 073, 95% CI 3 574 to 9 003; 37% of indirect costs) and unemployment (EUR 4 608, 95% CI 2 846 to 6 790 or USD 5 437, 95% CI 3 358 to 8 012; 33%). Sick leave was reported by 56 patients (26%) with a mean duration of 32.5 (95% CI 23.5 to 41.3) days within the last three months (eTable 1). Sixty percent (n=128) of the cohort was unemployed, the majority due to NMOSD/MOGAD (n=41, 32%). There was a negative correlation between employment and EDSS score ($p=-0.72$, 95% CI -0.89 to -0.35). Furthermore, the disease-related reduction in working time was 6.9 (95% CI 4.2 to 9.2) hours per week among employed patients.

Overall patient and societal economic burden

The mean total annual COI per patient was estimated at EUR 59 574 (95% CI 51 225 to 68 293; USD 70 297, 95% CI 60 445 to 80 586, Table 1). Direct medical costs accounted for 43%, direct non-medical costs for 34%, and indirect costs for 23% of the annual COI. On average, the out-of-pocket expenses of EUR 3 548 (95% CI 2 116 to 5 474; USD 4 187, 95% CI 2 497 to 6 459) per patient per year amounted to 6% of the annual COI (eTable 5). Annual costs rose with increasing EDSS ($p=0.56$, 95% CI 0.45 to 0.65), with the most notable increase in costs for informal care (Figure 2A).

Based on an estimated prevalence of NMOSD in Germany of 1.3/100,000, the annual burden from a societal perspective was calculated at EUR 64.2 (USD 75.8) million for Germany.²⁹

Cost of illness stratified by serostatus and disease duration

Total annual COI showed no differences between serogroups (eTable 6). Furthermore, the individual cost categories revealed no difference between serogroups except for the cost of outpatient diagnostic tests, which differed significantly ($p=0.01$) between AQP4-antibody positive NMOSD (EUR 248, 95% CI 200 to 304; USD 293, 95% CI 236 to 727) and MOGAD not fulfilling the IPND criteria (EUR 425, 95% CI 276 to 616; USD 502, 95% CI 326 to 727) in the group comparison, likely due to the average disease duration (Figure 1).

Considering the average costs, informal care has the largest impact on the costs of patients with AQP-4-positive NMOSD (EUR 18 220, 95% CI 14 239 to 22 686; USD 21 500, 95% CI 16 802 to 26 769), indirect costs were the largest cost driver in patients with MOGAD fulfilling the IPND criteria (EUR 19 391, 95% CI 9 409 to 31 506; USD 22 881, 95% CI 11 103 to 37 177), whereas the main cost driver in patients with MOGAD not fulfilling IPND criteria was medication costs (Figure 2B and eTable 6). There were no differences in total costs per patient for disease duration (eFigure 1).

Health-related quality of life (HRQoL)

In the EQ-5D-5L, over two thirds of all patients indicated slight to extreme problems regarding the following HRQoL dimensions: Pain/discomfort 79% (n=168), usual activities 69% (n=146), mobility 67% (n=142), and anxiety/depression 62% (n=132). Approximately every third patient (35%, n=75) stated an impairment in self-care. In all five dimensions the problems revealed a positive correlation with EDSS (mobility, $\rho=0.72$, 95% CI 0.65 to 0.79; self-care, $\rho=0.68$, 95% CI 0.60 to 0.75; usual activities $\rho=0.66$, 95% CI 0.57 to 0.73; pain/discomfort, $\rho=0.53$, 95% CI 0.42 to 0.63; anxiety/depression, $\rho=0.25$, 95% CI 0.11 to 0.38; Figure 3). The mean EQ-5D-5L index value was 0.693 (95% CI 0.65 to 0.73) using the German value set, with a negative correlation with disease severity (EDSS 0-3: 0.845, 95% CI 0.82 to 0.88; EDSS 3.5-6: 0.705, 95% CI 0.66 to 0.75; EDSS 6.5-8.5: 0.195, 95% CI 0.13 to 0.28; $\rho=-0.69$, 95% CI -0.76 to -0.61). Likewise, there was a decline in the global quality of life assessment using the EQ-VAS (all patients: 60.9, 95% CI 58.0 to 64.0; EDSS 0-3: 70.5, 95% CI 66.5 to 74.5; EDSS 3.5-6: 54.5, 95% CI 50.1 to 59.3; EDSS 6.5-8.5: 45.6, 95% CI 38.6 to 52.4; $\rho=-0.54$, 95% CI -0.63 to -0.42).

For serostatus and disease duration groups, no relevant differences were found within the five HRQoL dimensions (Figure 3B and eFigure 2). Moreover, neither index value nor EQ-VAS differed according to serostatus and disease duration groups. The mean EQ-5D-5L index values for the different serogroups are as follows: AQP4-antibody positive NMOSD 0.663

(95% CI 0.61 to 0.72), double seronegative NMOSD 0.761 (95% CI 0.67 to 0.85), MOGAD fulfilling the IPND criteria 0.745 (95% CI 0.63 to 0.85), and MOGAD not fulfilling the IPND criteria 0.757 (95% CI 0.65 to 0.86).

Predictors for COI and HRQoL

To identify factors that influence the total annual COI and HRQoL, cost categories and disease or patient characteristics were reviewed for any impact in a univariate analysis. In a subsequent generalized linear model analysis, the following independent predictors for COI were detected (Table 2A): EDSS (regression coefficients [RC]=6 563, 95% CI 7 068 to 18 286 up to an EDSS of 6.5 and 7 009, 95% CI 1 272 to 13 406 from an EDSS of 7, per EDSS point increase), need for care (RC=46 472, 95% CI 33 253 to 59 866), unemployment (RC=18 529, 95% CI 4 561 to 32 638), and attacks (RC=8 242, 95% CI 3 635 to 20 020). Accordingly, factors with significant impact on HRQoL were (Table 2B): EDSS (RC=-0.031, 95% CI -0.053 to -0.011 up to an EDSS of 6.5 and -0.046, 95% CI -0.058 to -0.033 from an EDSS of 7), need for care (RC=-0.110, 95% CI -0.173 to -0.054), unemployment (RC=0.052, 95% CI 0.012 to 0.091), disease duration (RC<0.001, 95% CI -0.003 to 0.004), care satisfaction (RC=-0.088, 95% CI -0.125 to -0.053), age at diagnosis (RC=-0.001, 95% CI -0.002 to 0.001), and investments at home (RC=-0.060, 95% CI -0.134 to -0.003).

Health care satisfaction

Nearly half of the patients stated they were very satisfied with health care, 40% were mostly satisfied, and 10% were moderately dissatisfied (eTable 7). One hundred twelve patients made additional suggestions for improvement: 25% wanted more information about the disease, its therapy, or research results. About a quarter (24%) asked for more psychological support, and 23% of patients would like to be treated more consistently and preferably by one physician.

Discussion

The evaluation of disease-related costs and quality of life is not only important for patients, their families, their physicians, and the society but also descriptively depicts the total burden of an illness in order to create a basis for decision-making of policy makers – especially in light of new and costly therapies.^{30,31} There are numerous respective studies in multiple sclerosis (MS) which have undoubtedly contributed to the optimization of diagnosis and quality of care in MS patients.³²⁻³⁵ To date, no sufficient data for NMOSD and MOGAD exist in this field. Thus, our aim was to address these issues with this study in order to improve the quality of care for patients suffering from this rare but serious disease.

Remarkably, we observed no differences of costs and quality of life regarding serostatus. Our study revealed an annual cost of illness (COI) for NMOSD/MOGAD of EUR 59 574 (95% CI 51 225 to 68 293; USD 70 297, 95% CI 60 445 to 80 586). When comparing this study with the largest corresponding study in a German MS cohort, COI for NMOSD/MOGAD shows an inflation-adjusted higher mean cost (EUR 41 207 or USD 48 624 for MS) – despite higher disease severity and patient age in the MS cohort.³⁵ Similarly, NMOSD/MOGAD displayed a poorer quality of life than MS when comparing the mean index value for quality of life assessments of these two study collectives (EQ-5D index value: 0.693 CHANCE^{NMO} vs. 0.756 for MS; best possible health condition: 1.0). In both diseases, there was a distinct inverse relationship between quality of life and EDSS.³⁵ Despite a higher EDSS as compared to our study population (5.0 vs. 3.5 in our study), a recent study of NMOSD in the U. S. did not show such pronounced reduction in quality of life with an EQ-5D mean index value of 0.738; however, patient numbers in that study were small (n=21 vs. 212 in the present study).⁵ These differences might be due to socio-cultural particularities or to their use of a mapping approach to calculate a country-specific value set. In contrast to the general population, the quality of life of patients suffering from NMOSD/MOGAD is substantially impaired: The

EQ-5D mean index value was 0.88 in a recently published representative German general population sample (n=4 998) and 0.938 in a German reference sample (n=3 552).^{36,37}

Interestingly, in the analysis of total COI and quality of life no relevant impact was found regarding the disease duration. This reflects the disease course because disability is mainly stable between relapses. Moreover, early treatment might prevent disability and might also have a positive side effect on COI. An annual cost increase for a one-point rise in EDSS of EUR 6 563 (95% CI 764 to 12 427) ending with an EDSS of 6.5 or EUR 13 261 starting with an EDSS of 7 emphasises this. In light of these data, a consequent, albeit expensive, attack treatment (EUR 8 242, 95% CI 3 635 to 20 020) with early application of apheresis techniques^{4,38} to avoid an accumulation of disability seems justified also from an economic point of view.

Informal care was the major cost driver at 28% of total COI. It reflects the immense burden on relatives and friends associated with the care of a loved one. These costs rise drastically with increasing disability. This information should be shared with patients and their caregivers, particularly as part of the decision process for an early start to therapy. Moreover, for clinicians, it should be an incentive to prevent long-term disability by providing the most appropriate therapy possible, and for scientists, to gain more profound knowledge about this rare disease in order to be able to treat it as optimally as possible in the future.

As this study was conducted in the era without approved standard medications, the costs for immunotherapeutics were moderate with 13% of the total COI. The new NMOSD therapeutics recently approved are considerably more expensive than the off-label therapies used so far and rank among the world's most expensive drugs.² For example, the annual medication costs for eculizumab in Germany are more than tenfold higher than the average total annual COI determined in this study. Recognizing the potentially dramatic disease course of this severe rare disease and its impact on HRQoL, our vision should be to make best

treatment options available to all our patients. Therefore, given the experience regarding the price increase of cancer drugs³⁹, controlled trials and registered-based studies to evaluate the cost-effectiveness of new NMOSD/MOGAD immunotherapeutics, especially in comparison with established treatments, are highly warranted.

The strength of this study, considering the rarity of the disease, is the large patient sample size. Furthermore, all clinical data were obtained from a cohort database where, for example, EDSS data were assessed by trained physicians and were not self-assessments by patients. The main limitation of our study is that the information on costs was based on patient reports from a questionnaire that inquired retrospective resource consumption with the risk of recall bias. Additionally, there is the possibility of a selection bias that more severely affected and/or visually impaired patients refused to participate in the extensive and time-consuming survey. In contrast, the high recruitment rate of 79% and broad EDSS distribution reinforces that the results of our study can be generalized. There were no obvious systematic reasons why 57 patients (6 patients were excluded from the original number of patients as mentioned in Figure 1) did not participate in the survey. We verified that there were no relevant differences between participants and non-participants, especially regarding the interesting predictor EDSS, but also, for example, disease duration, sex, and age. However, it cannot be excluded that, due to the nature of the study, different results would have been obtained if all identified patients had participated. Since our patient cohort had an earlier stage of disease compared to typical MS cohorts, there may be a bias in favor of more diagnostic procedures. Additionally, an earlier disease stage may disfavor the need for assistive devices for people with disabilities – although neither of these were relevant cost factors.

Conclusions

NMOSD and MOGAD are extremely costly for the individual, their families, and for society. The socio-economic impact depends on the severity of the disease, which has a strong

implication on the quality of life. These findings support an early, individually tailored, and cost-effective therapy to prevent long-term disability and preserve quality of life.

supplement --- <http://links.lww.com/WNL/B773>

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FIGURES

Figure 1. CHANCE^{NMO}-Study cohort categorized by serostatus, EDSS, and disease duration

Age and disease duration are shown as median with range in years, female sex and serostatus (AQP4 / neg. / MOG) are shown as percentage. Patient subgroups were defined based on serostatus, clinical disability (EDSS), and disease duration. Category boundaries are shown above. EDSS values of eight patients were missing. In one patient, the disease duration is unknown. In both cases, this had no effect on the representativeness of the group composition. Abbreviations: NMOSD, neuromyelitis optica spectrum disorders; MOG(AD), myelin oligodendrocyte glycoprotein immunoglobulin G antibody (associated disease); MOGAD IPND (+), myelin oligodendrocyte glycoprotein immunoglobulin G antibody positive disease fulfilling the International Panel for NMO Diagnosis criteria; MOGAD IPND (-), MOGAD not fulfilling the IPND criteria; EDSS, expanded disability status scale (score is shown as median with range); AQP4-IgG(+), aquaporin-4 immunoglobulin G antibody (positive patients); IPND, International Panel for NMO Diagnosis; neg., AQP4- and MOG-antibody negative NMOSD patients.

Figure 2. Mean annual costs per patient stratified by disease severity and serostatus

Mean total annual costs per patient per year of the entire study population and categorized according to disease severity groups (A) and serostatus (B). Abbreviations: EDSS, expanded disability status scale; EUR, Euros (2018); NMOSD, neuromyelitis optica spectrum disorders; AQP4-IgG(+), aquaporin-4 immunoglobulin G antibody (positive patients); MOGAD IPND (+), myelin oligodendrocyte glycoprotein immunoglobulin G antibody positive disease fulfilling the International Panel for NMO Diagnosis criteria 2015; MOGAD IPND (-), MOGAD not fulfilling the IPND criteria.

Figure 3. Level of problems experienced by patients stratified by disease severity (A) and serostatus (B)

Patients were able to provide levels on a scale from 0-5 (0 = no problems, 5 = unable / extreme problems) for each of the five dimensions of the EQ-5D-5L (EuroQoL five dimensions five levels questionnaire). Pain / discomfort between the AQP4-IgG (+) NMOSD and the double seronegative NMOSD group was the only dimension which differed significantly ($p=0.009$). Abbreviation: EDSS, expanded disability status scale; NMOSD, neuromyelitis optica spectrum disorders; AQP4-IgG(+), aquaporin-4 immunoglobulin G antibody (positive patients); MOGAD IPND (+), myelin oligodendrocyte glycoprotein immunoglobulin G antibody positive disease fulfilling the International Panel for NMO Diagnosis criteria 2015; MOGAD IPND (-), MOGAD not fulfilling the IPND criteria.

Table 1 Detailed mean annual costs per patient of the CHANCE^{NMO}-Study cohort stratified by disease severity

	Mean (95% CI)			
	All patients	EDSS 0 - 3	EDSS 3.5 - 6	EDSS 6.5 - 8.5
n ^a	212	101	70	33
Direct medical costs	25 600 (22 731 to 42 840)	18 259 (14 408 to 22 900)	21 237 (17 003 to 26 064)	54 477 (36 945 to 76 889)
Outpatient consultations	592 (462 to 739)	494 (316 to 751)	588 (434 to 773)	957 (533 to 1 450)
Outpatient hospital consultations	282 (233 to 332)	246 (170 to 320)	334 (238 to 431)	318 (198 to 441)
Inpatient hospital care	5 199 (3 904 to 6 615)	5 359 (3 634 to 7 370)	4 384 (2 604 to 6 523)	6 927 (2 907 to 12 403)
Medication incl. apheresis	9 786 (7 902 to 12 048)	8 527 (6 118 to 11 801)	9 259 (7 313 to 11 321)	15 693 (9 865 to 25 293)
Immunotherapy	7 757 (6 121 to 10 017)	7 127 (4 491 to 10 085)	6 803 (5 324 to 8 387)	12 626 (6 996 to 21 921)
Treatment of attacks	1 278 (771 to 1 829)	1 180 (430 to 2 235)	1 562 (642 to 2 632)	1 118 (422 to 1 949)
Symptomatic therapy	749 (530 to 1001)	220 (144 to 319)	894 (541 to 1 380)	1 946 (1 192 to 2 908)
Outpatient diagnostic tests	292 (243 to 342)	304 (237 to 373)	299 (227 to 372)	202 (105 to 317)
Rehabilitation	1 763 (1 005 to 2 608)	1 047 (455 to 1 715)	943 (390 to 1 691)	4 545 (1 711 to 8 461)
Therapeutic healing	3 493 (2 776 to 4 283)	1 335 (913 to 1 768)	3 672 (2 734 to 4 758)	8 950 (6 308 to 12 130)
Medical aids	519 (372 to 679)	54 (12 to 123)	739 (409 to 1 122)	1 289 (939 to 1 707)
Formal care	3 674 (1 807 to 6 393)	893 (133 to 1 948)	1 019 (287 to 1 977)	15 597 (6 277 to 30 863)
Direct non-medical costs	20 102 (15 762 to 24 624)	5 528 (3 193 to 8 598)	24 524 (17 993 to 31 705)	52 713 (37 728 to 70 112)
Informal care	16 460 (13 238 to 19 875)	5 210 (2 936 to 8 195)	19 763 (14 581 to 25 352)	40 477 (29 724 to 52 440)
Transportation	365 (266 to 487)	265 (160 to 389)	532 (287 to 838)	389 (183 to 649)
Investments home	2 563 (1 131 to 4 494)	53 (0 to 129)	3 104 (749 to 6 382)	9 649 (3 428 to 18 183)
Investments car	714 (205 to 1 320)	0	1 125 (111 to 2 382)	2 198 (251 to 4 678)
Indirect costs	13 872 (10 650 to 17 233)	11 205 (7 693 to 15 235)	14 275 (8 482 to 20 789)	22 497 (11 656 to 34 688)
Loss of salary for employed	3 168 (1 833 to 4 818)	3 444 (1 561 to 6 002)	2 534 (515 to 5 428)	3 933 (653 to 8 058)
Loss of salary for unemployed	4 608 (2 846 to 6 790)	889 (383 to 1 535)	7 541 (3 736 to 12 408)	9 365 (3 935 to 16 365)
Loss of salary as an indicator for productivity loss - days of sick leave	5 147 (3 029 to 7 630)	5 055 (2 815 to 7 722)	3 958 (730 to 8 024)	9 199 (1 432 to 18 751)
Loss of salary - working time reduction	949 (279 to 1 867)	1 817 (503 to 3 558)	242 (0 to 725)	0
Total costs	59 574 (51 225 to 68 293)	34 992 (28 570 to 41 937)	60 036 (48 399 to 72 369)	129 687 (101 946 to 160 336)

Mean costs (bootstrap lower to upper 95% confidence interval of the mean) per patient per year including out-of-pocket money expenses in Euros. Abbreviations: EDSS, expanded disability status scale.

^aEDSS values of eight patients were missing.

Table 2 Predictors of total cost of illness and health-related quality of life

A) Total annual costs vs.	Multiple Regression		GLM
	Change in total costs, €	95% bootstrap CI	p
EDSS	6 563	764 to 12 427	<0.001
EDSS >7	7 009	1 272 to 13 406	0.005
Need for care	46 472	33 253 to 59 866	<0.001
Unemployment	18 529	4 561 to 32 638	0.008
Disease duration	-109	-1 141 to 1 017	0.29
Care satisfaction	4 453	-5 108 to 15 281	0.56
Attacks	8 242	3 635 to 20 020	0.01
B) EQ-5D-5L index value vs.	Multiple Regression		GLM
	Change in index value	95% bootstrap CI	p
EDSS	-0.031	-0.053 to -0.011	<0.001
EDSS >7	-0.046	-0.058 to -0.033	<0.001
Need for care	-0.110	-0.173 to -0.054	<0.001
Unemployment	0.052	0.012 to 0.091	<0.001
Disease duration	<0.001	-0.003 to 0.004	<0.001
Care satisfaction	-0.088	-0.125 to -0.053	<0.001
Age at diagnosis	-0.001	-0.002 to 0.001	<0.001
Therapeutic healing	-0.001	-0.044 to 0.040	0.44
Medical aids	-0.046	-0.113 to 0.015	0.60
Transportation	-0.011	-0.057 to 0.035	0.74
Investments home	-0.060	-0.134 to 0.003	<0.001
Outpatient consultations	-0.055	-0.095 to -0.012	0.62

Results of two separate multiple regression models and generalized linear models (GLM) to identify the effects of non-normality. Due to missing values A, n=177 and B, n=174 cases were considered. The missing data do not systematically vary with independent variables and are therefore likely missing at random and thus do not imply a systematic bias in the data. Variables identified as predictors of total cost ($p<0.05$) were included in the final model of the regression analysis. The skewness in the independent variable is strongly correlated with higher EDSS values. The variable EDSS>7 therefore only contains values above 7, which were found to deliver systemically different estimates in the GLM regression. The factors need for care, unemployment, therapeutic healing, medical aids, transportation, and investments home are based on a dichotomous question (yes/no). Outpatient consultations were divided at the median of the study cohort (more or less than 5 outpatient consultations per year). Disease duration and age at diagnosis were referenced in years. Abbreviations: EDSS, expanded disability status scale; CI, bootstrap 95% confidence interval; COI, cost of illness.

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Costs and Health-Related Quality of Life in Patients With NMO Spectrum Disorders and MOG-Antibody–Associated Disease: CHANCE^{NMO} Study

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