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Inpatient care of neuromyelitis optica spectrum disorder in Germany: Nationwide analysis from 2010 to 2021

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Daniel Richter, Dirk Bartig, Lars Tönges, Tania Kümpfel, Carolin Schwake, Ralf Gold, Christos Krogias and Ilya Ayzenberg

Abstract

Background: Despite tremendous development in the treatment of neuromyelitis optica spectrum disorder (NMOSD), less is known about the characteristics of hospitalized patients and inpatient care utilization.

Objective: To investigate the development of inpatient NMOSD case numbers and implemented immunotherapies in the last decade in Germany.

Methods: We conducted a nationwide retrospective study using an administrative database of all hospitalized NMOSD patients between 2010 and 2021. We evaluated yearly data on case numbers, demographics, treatment regimens, and seasonal variations of apheresis therapy as a surrogate marker of severe relapse incidence.

Results: During the observational period case number of inpatients substantially increased (2010:$n = 463$, 2021:$n = 992$). The mean age was 48.1 ± 2.5 years (74% females). The pooled yearly rate of plasmapheresis/immunoadsorption was 14% (95% CI [13–15%]), without seasonal variations. Its application peaked in 2013 (18%, 95% CI [15–21%]) with decreasing trend since. Predominant immunotherapy was rituximab (40%, 95% CI [34–45%]), followed by tocilizumab (4%, 95% CI [3–5%]) since 2013 and eculizumab (4%, 95% CI [3–5%]) since 2020. Inpatient mortality ranged between 0% and 1% per year.

Conclusions: Inpatient case numbers of NMOSD substantially increased during the past decade, probably reflecting improving disease awareness. In parallel with the administration of highly effective therapies rate of apheresis therapies decreased. A stable apheresis rate over the year makes seasonal variations of the steroid-refractive relapses unlikely.

Keywords: NMOSD, Germany, inpatient care

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare severely disabling antibody-mediated disease of the central nervous system. Since the identification of autoantibodies targeting the astrocytic water channel protein aquaporin-4 (AQP4-abs), tremendous progress has been achieved in both understanding the underlying pathophysiological mechanisms and the development of effective NMOSD treatment.[1,2] The outcome after acute NMOSD relapse is often poor and requires prompt treatment initiation.[3–5] Advantages of the preventive off-label long-term immunotherapies with monoclonal antibodies rituximab and tocilizumab have been demonstrated in a retrospective series and recently proven by randomized trials.[6–10] In 2019, eculizumab, a highly effective C5 complement factor blocking monoclonal antibody, became the first approved NMOSD therapy, followed recently by satralizumab and inebilizumab.[11–14] Being a severely disabling disease, NMOSD causes a high burden on the affected patients and their families and requires a very extensive use of health care.[15,16]

The Neuromyelitis Optica Study Group (NEMOS) was founded in 2008 as a German-wide network of university neuroimmunological centers aiming to

Correspondence to:
Ilya Ayzenberg,
Department of Neurology, St Josef-Hospital Bochum, Ruhr University Bochum, Gudrunstraße 56, 44791 Bochum, Germany.
Email: **Ilya.Ayzenberg@ruhr-uni-bochum.de**

Daniel Richter,
Department of Neurology, St Josef-Hospital Bochum, Ruhr University Bochum, Bochum, Germany

Dirk Bartig,
Department of Neurology, St Josef-Hospital Bochum, Ruhr University Bochum, Germany

DRG Market, Osnabrück, Germany

Lars Tönges,
Department of Neurology, St Josef-Hospital Bochum, Ruhr University Bochum, Germany

Tania Kümpfel,
LMU Hospital, Ludwig Maximilian Universität München, Munich, Germany

Carolin Schwake,
Department of Neurology, St Josef-Hospital Bochum, Ruhr University Bochum, Germany

Ralf Gold,
Department of Neurology, St Josef-Hospital Bochum, Ruhr University Bochum, Germany

Christos Krogias,
Department of Neurology, St Josef-Hospital Bochum, Ruhr University Bochum, Germany

Ilya Ayzenberg,
Department of Neurology, St Josef-Hospital Bochum, Ruhr University Bochum, Germany

improve the treatment and care of patients with this rare disease. Despite rapidly increasing knowledge of the treatment, less is known about its effect on the real-world utilization of inpatient health care in NMOSD.

In the current study, we aimed to investigate changes in the hospitalization rate and inpatient mortality as well as the application of apheresis therapy and monoclonal antibodies in NMOSD in the past decade in Germany, using a comprehensive nationwide data registry.

Material and methods

This study followed the reporting guideline "Strengthening the Reporting of Observational Studies in Epidemiology."

Data source and study sample

This is a German nationwide cross-sectional study using retrospective administrative data from the diagnosis-related group (DRG) database (data transmission according to §21 KHEntgG, German Hospital Fees Act and §24 para. 2 KHG, German Hospital Financing Act; official data on file, source: Institut für das Entgeltsystem im Krankenhaus, InEK, www.g-drg.de). In Germany, all inpatient cases are encoded according to the German Version of the 10th International Classification of Diseases (ICD-10-GM) and operating and procedure keys (OPS codes) issued by the Federal Institute for Drugs and Medical Devices (BfArM). We included all hospitalized patients in Germany with the ICD-10 main diagnosis G36.0 (neuromyelitis optica, $n = 10{,}010$ cases) for each year from 2010 to 2021. NMOSD patients transferred once or multiple times from one hospital to another were censored to avoid double and multiple counting cases with main diagnosis G36.0 (excluding "discharge key 06").

In-hospital mortality was assessed using discharge key 07 (death during hospital stay). The number of plasmapheresis/immunoadsorption therapy was assessed using the corresponding OPS-codes for plasmapheresis (8–820) and immunoadsorption (8–821) in combination with a main diagnosis of ICD G36.0. The following OPS codes were used to assess immunosuppressive monoclonal antibody therapy: 6–001.h (rituximab); 6–005.m (tocilizumab); 6–003.hb (eculizumab).

For the treatment center analysis, we additionally extracted G36.0 cases from the mandatory structured quality reports of all German hospitals for the year 2019 (according to §136, 3; Social Code Book V of Germany). NEMOS centers were extracted from the NEMOS website (https://nemos-net.de/nemos-zentren.html; accessed on 13 May 2022).

Outcome

Primary outcomes were the number of hospital admissions, demographic characteristics, treatment with plasmapheresis or immunoadsorption as well as inpatient immunotherapy with rituximab, tocilizumab, or eculizumab and in-hospital mortality rate among NMOSD patients treated between 2010 and 2021. Seasonal dependency of plasmapheresis/immunoadsorption therapy was analyzed by extracting the corresponding data per month for the years 2019–2021.

Statistical analysis

Proportions are given for categorical variables and means and SDs for continuous variables. Absolute or relative changes in hospitalizations and treatment characteristics of NMOSD patients between the different periods of interest are given in integer numbers and percentages. Differences in means were calculated by *t*-test. Differences in proportions between the years of interest were calculated for the predefined outcomes under the random-effects model (DerSimonian-Laird). Within and in-between differences were analyzed with the Cochran test for heterogeneity and I^2 statistics. $p < .05$ was defined as the level of statistical significance.

Results

Case number development, demographics, and inpatient mortality

During the entire observational period, 10,010 cases were hospitalized with the primary diagnosis of NMOSD in Germany (Figure 1). Overall, hospitalized NMOSD cases were predominantly of the female sex (74% versus 26%) with a mean age of 48.1 ± 2.5 years. Female patients were slightly older compared to male patients, not reaching the level of significance (48.4 ± 2.5 versus 47.5 ± 2.7 years, $p = .058$). Analysis of the inpatient NMOSD case numbers per year demonstrated a substantial relative increase of 214% from 2010 to 2021 (2010: $n = 463$ patients; 2021: $n = 992$ patients). The strongest increase of 175% occurred between 2012 and 2016. After the peak in 2019, the number of inpatient case numbers decreased slightly in 2020 and 2021. Pooled case inpatient mortality was very low 0% (95% CI [0–0%], $I^2 = 40.23\%$) and ranged between 0% and 1% per year.

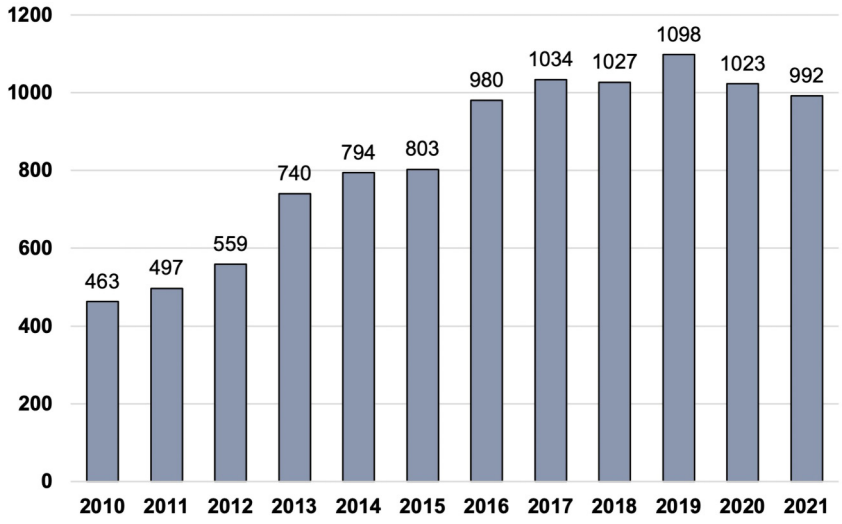

Figure 1. Case numbers of hospitalized NMOSD patients per year (2010–2021). Legend: Absolute case numbers of the NMOSD patients aggregated by year from 2010 to 2021.
NMOSD, neuromyelitis optica spectrum disorder.

Treatment location

In 2019, 210 out of 1576 hospitals reported inpatient treatment of at least one NMOSD patient according to the mandatory structured quality reports. More than half of the patients (57%) were treated in one of the 50 NEMOS centers.

Apheresis therapy

In 2010, 14% (95% CI [13–16%]) of the hospitalized NMOSD cases in Germany were treated with either plasmapheresis or immunoadsorption therapy. This proportion increased to 18% (95% CI [15–21%]) in 2013. Since then, there was a steady decrease concluding with 11% (95% CI: 9–13%) in 2021 (Figure 2). We observed a relative increase of 15% (95% CI [13–18%]) breaking this trend in 2020, the first Covid-19 pandemic year, only.

Proportion of patients treated with apheresis therapies in different months in relation to the whole analyzed period (2019–2021) is demonstrated in Figure 3. We found no seasonal dependency for the apheresis therapy, but for the decrease in December probably due to holidays and technical documentation issues.

Inpatient monoclonal antibody therapy

Over the entire period from 2010 to 2021, the predominant antibody regime in hospitalized NMOSD patients was rituximab (40%, 95% CI [36–45%]), followed by tocilizumab (4%, 95% CI [3–5%]) since 2013 and eculizumab (4%, 95% CI [3–5%]) since 2020. Inpatient use of rituximab and tocilizumab increased over the observational period until 2018 and decreased after 2020. Figure 2 summarizes the proportion of hospitalized NMOSD patients treated with rituximab and tocilizumab.

Discussion

This nationwide analysis of the inpatient care of NMOSD patients in Germany during the past decade revealed a substantial increase in the inpatient case numbers, which more than doubled from 2010 to 2016. We suppose that improving disease awareness among neurologists supported by the continuous education from NEMOS in Germany as well as better access to AQP4-IgG testing might contribute to the increase in the correct diagnosis in this period. Stabilization of the case numbers after 2017 probably reflects the natural prevalence of the disease while unmasking of patients previously misdiagnosed as MS could decrease. Hospitalized NMOSD patients were predominately female with a mean age of over 48.0 years, consistent with the epidemiological evidence of NMOSD demographics.[17] In contrast, we found a very low mortality rate among NMOSD patients in our study. This can be explained by the fact that our data reflects solely in-hospital mortality rates associated with the primary diagnosis of NMOSD, thus representing relapse-related mortality only. According to our data, more than half of the inpatients were treated at the specialized neuroimmunological NEMOS centers.

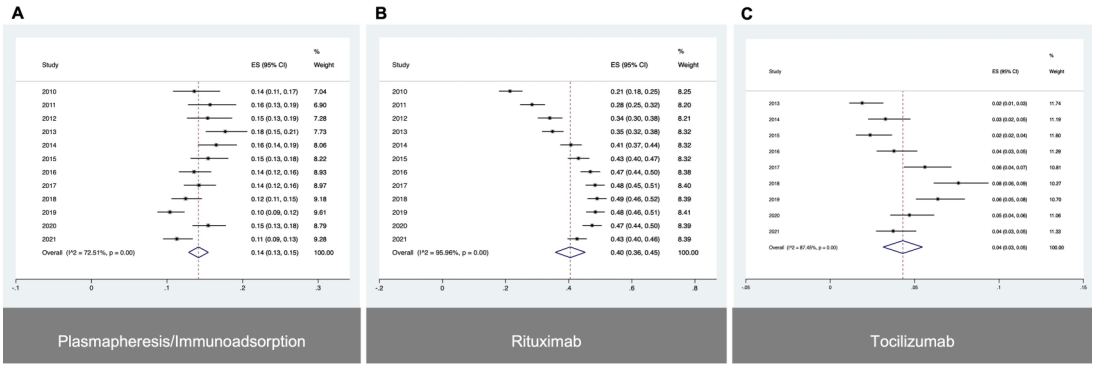

Figure 2. Treatment proportion per year for apheresis therapy, rituximab, and tocilizumab in hospitalized NMOSD patients 2010–2021; Legend: Estimation of proportion of inpatient case numbers treated with apheresis (plasmapheresis or immunoadsorption, A), rituximab (B), and tocilizumab (C) for each year from 2010 to 2021. Calculation of estimates including pooled estimates were performed under the random effects model.
NMOSD, neuromyelitis optica spectrum disorder.

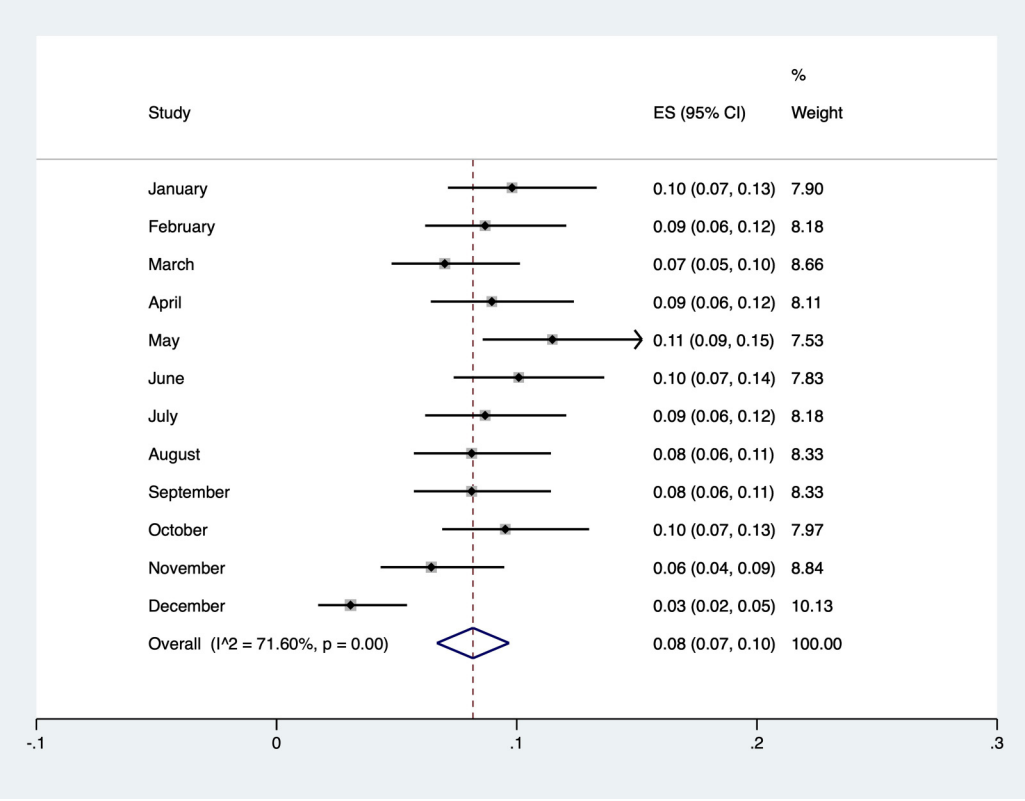

Figure 3. Seasonal trend of apheresis therapy. Estimation of the proportion of patients being treated with apheresis therapy (plasmapheresis or immunoadsorption) per month aggregated for the years 2019–2021. Calculation of estimates including pooled estimates were performed under the random effects model.

We observed an increase in both the absolute number and proportion of inpatients treated with apheresis therapy in the first years of the last decade that peaked in 2013. This trend can be attributed to mounting evidence indicating the direct pathogenic role of AQP4-IgG and antibody-dependent complement cytotoxicity, along with the accumulation of data on steroid-refractory severe NMOSD relapses. Although data on seasonal variations of relapses in NMOSD is controversial, our evaluation of the

monthly variations in the apheresis rate as a surrogate marker of severe relapses did not reveal any relevant seasonal differences.[18,19]

As evidence for the superiority of rituximab over former immunosuppressive drugs like azathioprine raised, the implementation and preferred administration of this highly effective therapy occurred from 2010 to 2019.[2,20,21] Despite being administered in a smaller number of cases, tocilizumab use also increased over time and has demonstrated high efficacy in NMOSD, including patients non-responding to rituximab.[7,10] Higher efficacy of monoclonal antibodies may have contributed to a decrease in the prevalence of steroid-refractory relapses and plasmapheresis/immunoadsorption rates observed after 2013.

Since 2019, the administration of both rituximab and especially tocilizumab started to decline in parallel to the approval of eculizumab. However, interpretation of the data from 2020 and 2021 should be performed with caution due to the Covid-19 pandemic and associated isolation of patients as well as the vaccination program, as previously reported.[22] A proportion of patients probably also delayed the rituximab administration due to an insufficient humoral vaccination response during anti-CD20 depletion that has been described numerously.[23]

This nationwide study has several strengths and limitations. We accessed comprehensive, nationwide, administrative data from Germany over a period of 12 years which are based on the documented diagnoses and procedures in the G-DRG system. There is a lack of available data on confounding factors, especially the severity of symptoms, pre-treatment conditions, and previous use of immunosuppressant drugs, which is the major drawback of this study. Moreover, despite characteristic demographic features, the proportion of AQP4- or MOG-IgG-positive patients remains unknown. Implementation of different codes depending on serological status (e.g., for AQP4-IgG positive NMOSD, seronegative NMOSD, and MOG-IgG-associated disease) would allow more precise and differentiated data analysis in the future, including proportion analysis of AQP4-IgG- or MOG-IgG-positivity in this nationwide cohort. Furthermore, it cannot be excluded with certainty that the lack of serological status in this database leads to an overrepresentation of NMOSD in this cohort. Nevertheless, this administrative data has high quality and accuracy because registration of all inpatient cases and procedures is a prerequisite to getting financial compensation. Its coding is closely controlled by medical services of the medical health insurance, providing almost 100% coverage of all hospitalized patients in Germany with a shallow risk of missing patients or double coding procedures and thus resulting in high validity and consistency.

In conclusion, Inpatient case numbers of NMOSD raised substantially during the past decade in Germany, probably due to better disease awareness. More than half of patients were treated in NEMOS centers. Despite being regularly used in NMOSD relapses, apheresis therapies became less common in the last 10 years in parallel to the application of highly effective immunotherapies with monoclonal antibodies. Future data will show whether the other newly approved drugs have advantages comparing to off-label standard of care and allow better disease control.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics

The study represents a secondary data analysis of data from the German Federal Statistical Office complying with the German data protection regulations. No informed consent or ethical approval was required.

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ORCID iDs

Carolin Schwake https://orcid.org/0000-0003-3669-7244
Christos Krogias https://orcid.org/0000-0003-2965-4051

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