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Original Research Paper

Influence of female sex and fertile age on neuromyelitis optica spectrum disorders

Nadja Borisow, Ingo Kleiter, Anna Gahlen, Katrin Fischer, Klaus-Dieter Wernecke, Florence Pache, Klemens Ruprecht, Joachim Havla, Markus Krumbholz, Tania Kümpfel, Orhan Aktas, Marius Ringelstein, Christian Geis, Christoph Kleinschnitz, Achim Berthele, Bernhard Hemmer, Klemens Angstwurm, Robert Weissert, Jan-Patrick Stellmann, Simon Schuster, Martin Stangel, Florian Lauda, Hayrettin Tumani, Christoph Mayer, Lena Zeltner, Ulf Ziemann, Ralf A Linker, Matthias Schwab, Martin Marziniak, Florian Then Bergh, Ulrich Hofstadt-van Oy, Oliver Neuhaus, Alexander Winkelmann, Wael Marouf, Lioba Rückriem, Jürgen Faiss, Brigitte Wildemann, Friedemann Paul, Sven Jarius, Corinna Trebst and Kerstin Hellwig; on behalf of NEMOS (Neuromyelitis Optica Study Group)

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Correspondence to:
N Borisow
NeuroCure Clinical Research Center and Clinical and Experimental Multiple Sclerosis Research Center, Department of Neurology, Charité–Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.
nadja.borisow@charite.de

Nadja Borisow
Florence Pache
NeuroCure Clinical Research Center and Clinical and Experimental Multiple Sclerosis Research Center, Department of Neurology, Charité University Medicine Berlin, Berlin, Germany

Friedemann Paul
NeuroCure Clinical Research Center and Clinical and Experimental Multiple Sclerosis Research Center, Department of Neurology, Charité University Medicine Berlin, Berlin, Germany/ Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine and Charité University Medicine Berlin, Berlin, Germany

Ingo Kleiter
Anna Gahlen
Kerstin Hellwig
Department of Neurology, St. Josef Hospital, Ruhr University Bochum, Bochum, Germany

Katrin Fischer
Jürgen Faiss
Department of Neurology, Asklepios Fachklinikum Teupitz, Teupitz, Germany

Klaus-Dieter Wernecke
CRO SOSTANA GmbH and Charité University Medicine Berlin, Berlin, Germany

Klemens Ruprecht
Department of Neurology and Clinical and Experimental Multiple Sclerosis Research Center, Charité University Medicine Berlin, Berlin, Germany

Joachim Havla
Markus Krumbholz
Tania Kümpfel
Institute of Clinical Neuroimmunology, Medical Campus Grosshadern,

Abstract

Background: Gender and age at onset are important epidemiological factors influencing prevalence, clinical presentation, and treatment response in autoimmune diseases.

Objective: To evaluate the impact of female sex and fertile age on aquaporin-4-antibody (AQP4-ab) status, attack localization, and response to attack treatment in patients with neuromyelitis optica (NMO) and its spectrum disorders (neuromyelitis optica spectrum disorder (NMOSD)).

Methods: Female-to-male ratios, diagnosis at last visit (NMO vs NMOSD), attack localization, attack treatment, and outcome were compared according to sex and age at disease or attack onset.

Results: A total of 186 NMO/SD patients (82% female) were included. In AQP4-ab-positive patients, female predominance was most pronounced during fertile age (female-to-male ratio 23:1). Female patients were more likely to be positive for AQP4-abs (92% vs 55%; $p<0.001$). Interval between onset and diagnosis of NMO/SD was longer in women than in men (mean 54 vs 27 months; $p=0.023$). In women, attacks occurring ⩽40 years of age were more likely to show complete remission ($p=0.003$) and better response to high-dose intravenous steroids ($p=0.005$) compared to woman at >40 years.

Conclusion: Our data suggest an influence of sex and age on susceptibility to AQP4-ab-positive NMO/SD. Genetic and hormonal factors might contribute to pathophysiology of NMO/SD.

Keywords: Neuromyelitis optica, sex, age factors, aquaporin 4

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Introduction

Neuromyelitis optica (NMO) and its spectrum disorders (neuromyelitis optica spectrum disorder (NMOSD)) are autoimmune disorders of the central nervous system, diagnostically characterized and pathophysiologically linked with the presence of anti-aquaporin-4-antibodies (AQP4-abs) in the majority of patients.[1] The female-to-male ratio markedly exceeds 3:1[2,3] and reaches 8–9:1 in some AQP4-ab-positive populations.[4] With clear female predominance in most studies, sex emerges as one of the most important factors of susceptibility to NMO/SD.

Sex may also influence clinical features, disease course, and severity in NMO/SD. Previous studies showed a female predominance in AQP4-ab-seropositive patients.[4,5] Male NMO patients were more likely to follow a monophasic disease course in a predominantly Caucasian cohort.[6]

Over the lifespan, women undergo tremendous hormonal changes, especially during puberty, pregnancy, and menopause. These hormonal changes might influence susceptibility, course, and severity of autoimmune diseases. Other autoimmune disorders, for

example, systemic lupus erythematosus (SLE)[7] or multiple sclerosis (MS)[8] show a clear female predominance. In SLE, female-to-male ratio is most pronounced during fertile age.[7] In MS, male patients are older, more likely to develop myelopathy, and suffer from faster progression than female patients.[9]

Increase in knowledge on sex- and age-specific aspects might be helpful for prognostic assessment and open insights in the susceptibility and pathophysiology of NMO/SD.

In this study, we investigated for the first time if there are (1) differences in the female-to-male ratio between age groups in NMO/SD and (2) differences in symptoms of attacks and treatment response in female patients during and beyond reproductive age.

Methods

Patients were identified using the registry of the German Neuromyelitis Optica Study Group (NEMOS, www.nemos-net.de), a nationwide open association of neurological centers interested mainly in adult NMO/SD (34 German university and academic teaching hospitals). Pediatric centers were not participating in the current study. The study was approved by the institutional review boards of the participating academic centers and conducted in accordance with the German data protection law. Between January 2012 and March 2013, we retrospectively analysed data of 215 NMO/SD patients which were collected cross-sectionally in a standardized manner by two neurologists visiting the contributing centers in a "flying doctor" approach.

Inclusion criterion was a diagnosis of NMO according to Wingerchuk et al.'s criteria[10] ("NMO") or of isolated or recurrent AQP4-ab-positive optic neuritis (ON) or myelitis ("NMOSD").[11] Some patients of our cohort were initially misdiagnosed as MS. To avoid misclassification, the diagnosis at the most recent visit prior to data collection was used for patient stratification. Demographic characteristics, diagnoses, duration of clinical observation, clinical attacks, attack treatment, and attack outcome were analysed in a stratified fashion according to sex and to fertile age in women.

The vast majority of girls experience menarche around the age of 15 years, and only a very small proportion of births occurs before the 15th or after the 40th year of age.[12] Moreover, menopause is very unlikely to occur before the age of 40 years; the risk of natural menopause before age 40 is approximately 1%.[13] Therefore, we defined fertile age between 15 and 40 years. Time to diagnosis, AQP4-ab status, disease classification, and the annualized relapse rate (ARR) were analysed according to age at disease onset. Attack-related factors like clinical presentation and attack remission were at first analysed according to age at attack onset. Attack treatment was escalated up to four times. Only first treatment courses for attacks were included in the analysis of treatment responses.

Of 215 patients recorded in the database, 29 patients were excluded due to missing data or because they did not meet inclusion criteria. Finally, data from 186 patients were available for statistical analysis (Figure 1). These patients had a total of 1124 attacks, but in 253 attacks, documentation on treatment and/or outcome was insufficient. Therefore, only 871 attacks were included in the final analysis.

Demographic data, attack characteristics, therapies, and the short-term remission status of the complete cohort were previously described.[14]

The statistical analysis was conducted in two steps. First, we analysed patient-related data such as age at onset, time between onset and diagnosis, AQP4-ab serostatus, disease classification, and ARR. Those analyses were accomplished using the exact chi-square test or the exact Mann–Whitney test, accordingly. Second, in order to adjust for intraindividual correlations within patients, we applied generalized estimating equations (GEEs)[15] with patient as statistical unit for attack localization (type of attack) and attack remission. In GEE, odds ratios for risk factors and corresponding 95% confidence intervals (95% CIs) were given. Statistical analyses were performed using IBM© SPSS© Statistics, Version 23, ©Copyright 1989, 2010 SPSS Inc., an IBM Company. Results are shown as median and interquartile range (IQR) or mean ± standard deviation (SD) when normal distribution wasn't rejected. Statistical significance was set at a two-sided $p < 0.05$. Our study was an exploratory analysis; therefore, no correction for multiple comparisons was performed.

Results

Female-to-male ratio in different age groups

We identified a total of 186 patients (Figure 1). Age at disease onset ranged between 15 and 65 years in more than 90% of the patients. The youngest patient was 8 years old at disease onset, whereas the oldest developed first symptoms at an age of 79 years (Table 1). In

Ludwig Maximilians University of Munich, Munich, Germany

Orhan Aktas
Marius Ringelstein
Department of Neurology, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

Christoph Kleinschnitz
Department of Neurology, University Hospital Essen, Essen, Germany

Christian Geis
Department of Neurology, University Hospital of Würzburg, Würzburg, Germany/Hans-Berger Department of Neurology and Center for Sepsis Control and Care (CSCC), Jena University Hospital, Jena, Germany

Achim Berthele
Department of Neurology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

Bernhard Hemmer
Department of Neurology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany/ Munich Cluster for Systems Neurology (SyNergy), Technische Universität München, Munich, Germany

Klemens Angstwurm
Robert Weissert
Department of Neurology, University Hospital Regensburg, Regensburg, Germany

Jan-Patrick Stellmann
Institute of Neuroimmunology and MS (INIMS), University Medical Center Hamburg-Eppendorf, Hamburg, Germany/ Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Simon Schuster
Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Martin Stangel
Department of Clinical Neuroimmunology and Neurochemistry and Department of Neurology, Hannover Medical School, Hannover, Germany

Florian Lauda
Department of Neurology, University of Ulm, Ulm, Germany

Hayrettin Tumani
Department of Neurology at RKU and Specialty Clinic of Neurology Dietenbronn, University of Ulm, Ulm, Germany

Christoph Mayer
Department of Neurology, Goethe University Frankfurt, Frankfurt, Germany

Lena Zeltner
Ulf Ziemann
Department of Neurology and Stroke and Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany

Ralf A Linker
Department of Neurology, Friedrich-Alexander University Erlangen-Nüremberg, Erlangen, Germany

Matthias Schwab
Hans-Berger Department of Neurology, Jena University Hospital, Jena, Germany

Martin Marziniak
Department of Neurology, University of Münster, Münster, Germany/ Department of Neurology and Neurological Intensive Care, Isar-Amper-Clinic, Munich-East, Haar, Germany

Florian Then Bergh
Department of Neurology, Leipzig University, Leipzig, Germany

Ulrich Hofstadt-van Oy
Department of Neurology, Klinikum Bayreuth, Bayreuth, Germany/ Department of Neurology, Klinikum Westfalen, Dortmund, Germany

Oliver Neuhaus
Department of Neurology, SRH Krankenhaus Sigmaringen, Sigmaringen, Germany

Alexander Winkelmann
Department of Neurology, University of Rostock, Rostock, Germany

Wael Marouf
Department of Neurology, HELIOS Hanseklinikum Stralsund, Stralsund, Germany

Lioba Rückriem
Department of Neurology, MediClin Hedon Klinik, Lingen, Germany

Brigitte Wildemann
Sven Jarius
Department of Neurology, Heidelberg University, Heidelberg, Germany

Corinna Trebst
Department of Neurology, Hannover Medical School, Hannover, Germany

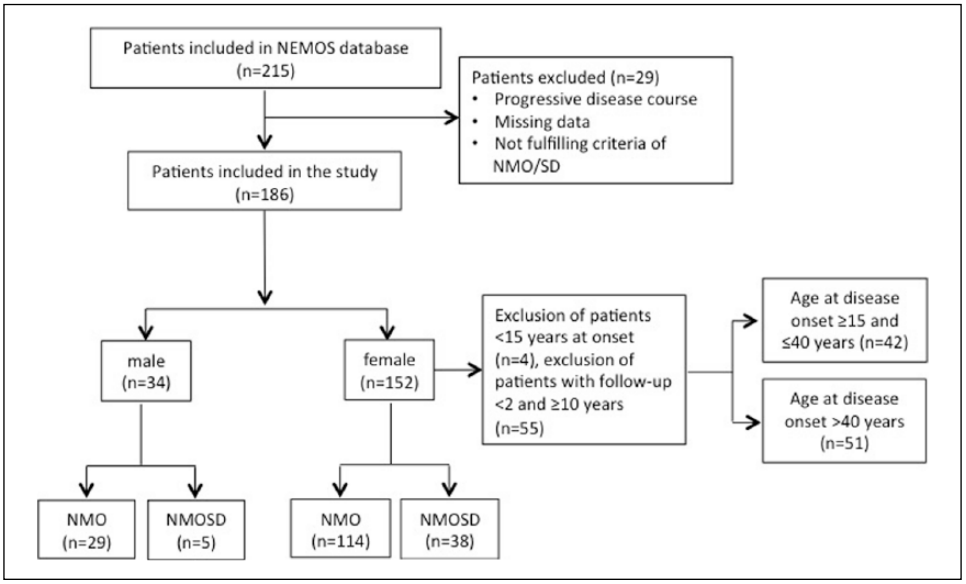

Figure 1. Flow chart of the patients enrolled in the study.

Table 1. Demographic characteristics.

		n (%)
Sex	Female	152/186 (82)
	Male	34/186 (18)
Age at onset (complete cohort, range: 8–79)	<15 years	6/186 (3)
	15–40 years	89/186 (48)
	41–65 years	83/186 (45)
	>65 years	8/186 (4)
Age at onset (women only)	<15 years	4/152 (3)
	15–40 years	78/152 (51)
	41–65 years	65/152 (43)
	>65 years	5/152 (3)
Age at onset (men only)	<15 years	2/34 (6)
	15–40 years	10/34 (29)
	41–65 years	19/34 (56)
	>65 years	3/34 (9)

all, 152 (82%) were female. Female-to-male ratio was 4.5:1 in the total cohort, 8:1 in patients with disease onset in the fertile age, and 3:1 in patients older than 40 years at disease onset (Figure 2). In the small subgroup of patients <15 years at onset ($n=6$), female-to-male ratio was 2:1. In 183/186 patients (98%), information about AQP4-ab-status were available. Out of these, 156 (85%) were AQP4-ab-positive. In AQP4-ab-positive patients, female-to-male ratios were 3:1, 23:1, and 5:1 for age groups <15, 15–40, and >40 years, respectively. In contrast, in AQP4-ab-negative patients ($n=27$, 15%), the female-to-male ratios were 1:1.2 for age groups 15–40 and >40 years, respectively. As in AQP4-ab-negative patients only one patient was younger than 15 years at onset, a female-to-male ratio was not applicable.

Comparison between female and male patients

Mean duration of clinical observation in female and male patients was 47 (23–107) versus 68 (39–117) months ($p=0.054$). Women tended to be younger (mean 39 ± 14 years) than men (mean 44 ± 17 years, $p=0.075$) at disease onset. The majority of both men and women showed a relapsing disease course (91% and 94%, respectively), while in the remaining patients, a monophasic disease course was recorded. In women, the duration until the diagnosis of NMO/SD had been confirmed was longer than in men ($p=0.023$). AQP4-abs were more frequently detected in female than in male patients ($p<0.001$; Table 2).

The number of female and male patients receiving disease-modifying treatments (DMTs) is shown in Table 2. The median number of DMT per patient was 2 (range 1–8). Mean DMT interval was 441 (±421) days.

A total of 28% of all attacks presented as ON and 59% as myelitis. The remaining attacks showed either simultaneous ON and myelitis or symptoms different from ON or myelitis. No differences in the frequencies of ON and myelitis attacks were found between male and female patients (Table 2).

In almost all patients (181/186, 97%), at least once an acute attack was treated with high-dose intravenous

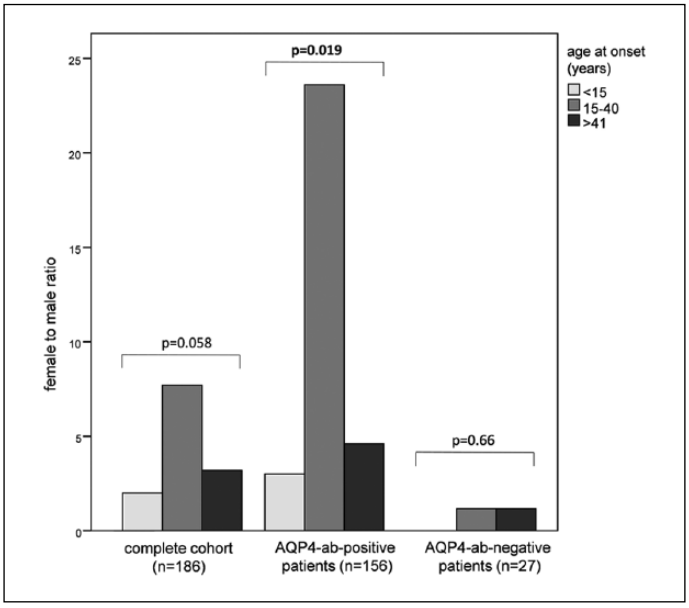

Figure 2. Age distribution of female-to-male ratio.

steroids (HD-S) as first-line treatment. A total of 27 patients (15%) received therapeutic plasma exchange (TPE) and 7 (4%) received immunoadsorption as first treatment course of at least one attack. Frequencies of applied first-line therapies did not differ between men and women. No differences in attack localization and in attack outcome for any of the applied first treatment courses were found between male and female patients (Table 2).

Comparison between women of fertile age and women beyond fertile age

Female patients younger than 15 years ($n=4$) were not included in the analysis. To ensure a similar clinical observation period in both groups, female patients with an observation period of <2 and ⩾10 years ($n=55$) were excluded from the analysis. Among the remaining 93 women, 42 were between 15 and 40 years old at disease onset (median clinical observation 74 (40–88) months). A total of 51 female patients were older than 40 years (median clinical observation 51 (40–72) months; $p=0.08$) at disease onset. A total of 468 attacks were recorded in these patients.

Women ⩽40 years at disease onset were more likely to fulfill Wingerchuk's criteria compared to women >40 years ($p=0.008$). No differences were detected in AQP4-ab status, ARR, and time between initial manifestation and diagnosis (Table 3).

We found no differences in the use of first-line attack therapy between women ⩽40 years at disease onset and female patients >40 years.

Attacks in women occurring at an age of 40 years or lower showed a higher frequency of complete attack remission ($p=0.003$) and a better response to HD-S ($p=0.005$). The comparison of response to TPE between attacks occurring at an age of ⩽ and >40 years missed significance. No differences in attack localization were detected (Table 3).

In order to differentiate between age and sex effects, we also explored the male patients. Male patients between 15 and 40 years at disease onset ($n=10$) did not differ from male patients >40 years ($n=22$) with regard to ARR and disease classification (NMO vs NMOSD). No differences in attack localization, attack outcome, or treatment response to HD-S and TPE were detected in attacks occurring at an age of 40 years or lower compared to attacks occurring at an age of >40 years (Table 4).

Discussion

In our cohort of predominantly Caucasian NMO/SD patients, we found a significant female preponderance. A total of 82% of our patients were female, which is in line with the results of other NMO cohorts.[3] The female-to-male ratio at disease onset was most pronounced in the reproductive age between 15 and 40 years (8:1 vs 2:1 and 3:1, respectively).

Table 2. Comparison between female ($n=152$) and male ($n=34$) NMO/SD patients.

	Female ($n=152$) (reference)	Male ($n=34$)	p-value	Odds ratio (95% CI)
Age at onset (years (±SD))	39 (±14)	44 (±17)	0.08[a]	
Time between onset and diagnosis (months)	54 (±80)	27 (±42)	**0.02**[a]	
AQP4-ab-positive	138 (92%)	18 (55%)	**<0.001**[b]	
Annualized relapse rate (clinical observation >1 year)	0.9 (0.6–1.4)	0.9 (0.6–1.4)	0.90[a]	
Disease classification				
NMO[c]	114/152 (75%)	29/34 (85%)	0.20[b]	
NMOSD	38/152 (25%)	5/34 (15%)		
Disease-modifying treatments (patients receiving treatment *n*)				
Rituximab	62	12		
Azathioprine	50	4		
Mitoxantrone	29	9		
Interferon-beta	26	5		
Glatiramer acetate	17	1		
Cyclophosphamide	16	0		
Steroids per os	14	2		
Steroids intrathecal	7	2		
Others[d]	29	8		
Type of attack ($n=871$ attacks in 185 patients)				
Optic neuritis (ON)	213/731 (29)	35/140 (25)	0.69[e]	1.049 (0.825–1.34)
Myelitis	425/731 (58)	92/140 (66)		
ON + myelitis	77/731(11)	12/140 (8)		
Other	16/731 (2)	1/140 (1)		
Remission overall ($n=871$ attacks in 185 patients)				
Complete	147/731 (20)	26/140 (19)	0.69[e]	0.888 (0.496–1.59)
Incomplete/no	573/731 (78)	112/140 (80)		
MD	11/731 (2)	2/140 (1)		
Remission HD-S (first pulse) ($n=693$ attacks in 181 patients)				
Complete	96/575 (17)	22/118 (19)	0.76[e]	1.102 (0.591–2.06)
Incomplete/no	471/575 (82)	94/118 (80)		
MD	8/575 (1)	2/118 (1)		
Remission TPE (first cycle) ($n=63$ attacks in 28 patients)				
Complete	18/55 (33)	1/8 (13)	0.76[e]	0.704 (0.075–6.57)
Incomplete/no	36/55 (65)	7/8 (87)		
MD	1/55 (2)	0/8 (0)		
Remission immunoadsorption (first cycle) ($n=9$ attacks in seven patients)				
Complete	0/8 (0)	1/1 (100)	NA	
Incomplete/no	8/8 (100)	0/1 (0)		

HD-S: high-dose intravenous steroids; TPE: therapeutic plasma exchange; NA: not applicable; MD: missing data; CI: confidence interval; SD: standard deviation; NMO: neuromyelitis optica; NMOSD: neuromyelitis optica spectrum disorder; AQP4-ab: aquaporin-4 antibody.

[a]Mann–Whitney *U* test was performed to compare continuous data.

[b]Categorical data were compared using exact chi-square test.

[c]NMO fulfilling Wingerchuk's criteria.[10]

[d]Alemtuzumab, cyclosporine A, fingolimod, intravenous immunoglobulins, steroids intravenous, tocilizumab, natalizumab, mycophenolate mofetile, and methotrexate.

[e]To adjust for intraindividual dependencies we additionally applied generalized estimating equations (GEEs) with patient as statistical unit for analysis. Shown are median and interquartile range (IQR) or mean ± SD when normally distributed.

Table 3. Comparison between female NMO/SD patients of fertile age and beyond fertile age at onset.

	Age between 15 and 40 years ($n=42$)	Age >40 years ($n=51$) (reference)	p-value	Odds ratio (95% CI)
Time between onset and diagnosis (months)	31 (±31)	22 (±21)	0.25[a]	
AQP4-ab-positive	38/42 (91%)	49/51 (96%)	0.27[b]	
Annualized relapse rate (clinical observation ⩾2 and <10 years)	1.1 (±0.7)	1.0 (±0.6)	0.98[a]	
Disease classification				
NMO[c]	36/42 (86%)	31/51 (61%)	**0.008**[b]	
NMOSD	6/42 (14%)	20/51 (39%)		
Type of attack ($n=468$ attacks in 93 patients)				
Optic neuritis (ON)	69/226 (31)	58/242 (24)	0.10[d]	0.803 (0.618–1.04)
Myelitis	129/226 (57)	155/242 (64)		
ON + myelitis	19/226 (8)	28/242 (12)		
Others	9//226 (4)	1/242 (0.4)		
Remission overall ($n=468$ attacks in 93 patients)				
Complete	57/226 (25)	29/242 (12)	**0.003**[d]	**0.361 (0.185–0.705)**
Incomplete/no	136/226 (60)	189/242 (78)		
MD	33/226 (15)	24/242 (10)		
Remission HD-S (first pulse) ($n=338$ attacks in 93 patients)				
Complete	32/155 (21)	19/183 (10)	**0.005**[d]	**0.353 (0.172–0.728)**
Incomplete/no	108/155 (70)	156/183 (85)		
MD	15/155 (10)	9/183 (5)		
Remission TPE (first cycle) ($n=38$ attacks in 15 patients)				
Complete	15/18 (83)	0/20 (0)	NA	No solution for GEE
Incomplete/no	2/18 (11)	19/20 (95)		
MD	1/18 (6)	1/20 (5)		
Remission immunoadsorption (first cycle) ($n=$ seven attacks in five patients)				
Complete	0/7 (0)	0/0 (0)	NA	
Incomplete/no	7/7 (100)	0/0 (0)		

HD-S: high-dose intravenous steroids; TPE: therapeutic plasma exchange; NA: not applicable; MD: missing data; CI: confidence interval; SD: standard deviation; NMO: neuromyelitis optica; NMOSD: neuromyelitis optica spectrum disorder; AQP4-ab: aquaporin-4 antibody.
To ensure a similar duration of clinical observation in both groups, only women with an observation period of >2 and ⩽10 years were included in the analysis.
[a]Mann–Whitney *U* test was performed to compare continuous data.
[b]Categorical data were compared using exact chi-square test.
[c]NMO fulfilling Wingerchuk's criteria.[10]
[d]To adjust for intraindividual dependencies, we additionally applied generalized estimating equations (GEEs) with patient as statistical unit for analysis. Shown are median and interquartile range (IQR) or mean ± SD when normally distributed.

Many autoimmune diseases show a female predominance, for example, SLE and MS. As in our NMO/SD study, female preponderance is also marked during fertile age in SLE.[16] Studies in pediatric MS showed a balanced sex ratio in children <11 years[17] and highest female-to-male ratios in patients between 12 and 15 years,[17,18] suggesting that hormonal changes during puberty have an impact on MS onset; female-to-male ratio declined with increasing age and showed a male excess in MS patients with disease onset after the 50th year of age.[18]

Previous studies described a strong female predominance in pediatric NMO.[2,19] In our cohort, the number of patients with pediatric onset was very low ($n=6$). We cannot rule out that the female-to-male ratio of 2:1 found in this age group is due to low patient numbers or to differences in ethnic background between studies.

Diagnosis of NMO/SD was significantly delayed in women compared to men. Being misdiagnosed with MS was the main reason for this delay. Prior to the

Table 4. Comparison between male NMO/SD patients between 15 and 40 years and >40 years of age.

	Age between 15 and 40 years ($n=10$)	Age >40 years ($n=22$)	p-value	Odds ratio (95% CI)
Time between onset and diagnosis (months)	37 (±56)	16 (±26)	0.41[a]	
AQP4-ab-positive	3 (30%)	14 (64%)	0.12[b]	
Annualized relapse rate (clinical observation >1 year)	1.0 (0.7–1.5)	1.0 (0.7–1.8)	0.62[a]	
Disease classification				
NMO[c]	10 (100%)	18 (82%)	0.15[b]	
NMOSD	0 (0%)	4 (18%)		
Type of attack ($n=135$ in 33 patients)				
Optic neuritis (ON)	14/51	17/84	0.71[d]	0.917 (0.582–1.45)
Myelitis	32/51	59/84		
ON + myelitis	5/51	7/84		
Other	0/51	1/84		
Remission overall ($n=135$ attacks in 33 patients)				
Complete	13/51 (25)	10/84 (12)	0.06[d]	0.371 (0.134–1.02)
Incomplete/no	37/51 (73)	73/84 (87)		
MD	1/51 (2)	1/84 (1)		
Remission HD-S (first pulse) ($n=114$ attacks in 32 patients)				
Complete	11/45 (24)	9/69 (13)	0.12[d]	0.417 (0.139–1.255)
Incomplete/no	33/45 (73)	59/69 (86)		
MD	1/45 (2)	1/69 (1)		
Remission TPE (first cycle) ($n=$ eight attacks in five patients)				
Complete	0/0	1/8 (13)	NA	
Incomplete/no	0/0	7/8 (87)		
Remission immunoadsorption (first cycle) ($n=$ one attack in one patient)				
Complete	1/1 (100)	0/0 (0)	NA	
Incomplete/no	0/1 (0)	0/0 (0)		

HD-S: high-dose intravenous steroids; TPE: therapeutic plasma exchange; NA: not applicable; MD: missing data; CI: confidence interval; SD: standard deviation; NMO: neuromyelitis optica; NMOSD: neuromyelitis optica spectrum disorder; AQP4-ab: aquaporin-4 antibody; GEE: generalized estimating equation.
Shown are median and interquartile range (IQR) or mean ± SD when normally distributed.
[a]Exact Mann–Whitney test.
[b]Exact chi-square test.
[c]NMO fulfilling Wingerchuk criteria.[10]
[d]GEE analysis.

availability of AQP4-ab testing, up to 42% of NMO patients were misdiagnosed as MS.[4] The higher prevalence of MS compared to NMO and the fact that NMO was considered to be a form of MS might be the reasons for this finding. We did not observe differences in ARR between male and female patients; therefore, frequency of attacks does not serve as explanation for differences in duration between onset and diagnosis. Given the severity of attacks in NMO/SD and the differences in treatment response between NMO/SD and MS,[20,21] an early correct diagnosis is essential.[22]

Besides prevalence, clinical features in autoimmune diseases are known to be influenced by sex. In our cohort, AQP4-abs were more frequent in female patients. Other studies confirmed a female predominance among seropositive patients.[4,5] Sex differences in antibody serum status are also known in other autoimmune diseases. Of note, anti-SSA and anti-SSB were detected more often in women with SLE,[23] whereas anti-dsDNA were shown to be more prevalent among male patients.[24] Thus, a female predominance is not necessarily found in antibody-mediated autoimmune diseases. The reasons for sex differences in the prevalence of autoreactive autoantibodies are not fully understood, but they might be of importance as NMO/SD possibly takes a more severe course in seropositive patients.[4,25,26]

Sex differences in predisposition and course of autoimmune diseases are, first and foremost, assumed to be based on differences in immunocompetence and immune reactivity. Hormonal factors, for example, differences in circulating sex hormones or changes in hormone receptor expression are supposed to be involved in sex differences in autoimmune diseases.[27] Moreover, differences in major histocompatibility complex (MHC) risk alleles, in genetic imprinting, in the transcription of inflammation-related genes, and in the responsiveness to environmental factors, for example, infections, smoking, or sun exposure, have to be taken into consideration.[28,29] Women are known to show significantly stronger immune responses to infections and vaccination.[30] Immunological tolerance might be more strongly controlled by hormonal factors, especially before menopause and during pregnancy.

We chose the cutoff of 40 years to compare female patients during and beyond fertile age. In general, menopause starts at an age of 50 years and is characterized by the last menstrual period. However, a decline in fertility already starts up to 10 years before, as pregnancy rates are continuously decreasing after the age of 40 years.[12] The decline in reproductive function of the ovaries is accompanied by various hormonal changes, for example, of growth hormone, follicle-stimulating hormone, and estradiol,[31] which might have an influence on autoimmunity.[32,33]

In women, response to attack treatment was age related. Complete remission and a better response to treatment with HD-S were found more frequently at an age <40 years. We did not observe the same age dependency in male patients, which might primarily be due to the small sample size of the male group. In other diseases, for example, in MS, age seems to influence attack severity and recovery.[34] Some studies described an overall better recovery from MS attacks in young-onset patients,[18] whereas others found no differences or even reverse results.[35] However, in these studies, the influence of different treatment regimens was not explicitly considered.

The retrospective design of our study is a potential limitation. However, NMO/SD is a very rare disorder and was recognized as a disease entity distinct from MS only a few years ago. Thus, to date, only retrospective analyses allow to investigate epidemiologic and clinical features in large cohorts of NMO/SD patients. Another limitation is the small sample size of the male and pediatric subgroups in our cohort. Although the NEMOS cohort is one of the largest NMO/SD cohorts published to date, our study includes only 34 male patients and six children <15 years. The cutoffs for fertile age used in this study are necessarily arbitrary (15–40 years), as the beginning of menstrual irregularities was not systematically recorded in our study. Desirable for further studies would be the use of time-dependent covariates (exact date of last and first menses) in the statistical analysis. Finally, no structured pregnancy data were recorded in our study, which is another limitation.

As a major strength and different from previous studies, our data are derived from a very large cohort from a country where almost everybody has access to the healthcare system, reducing a bias toward more severely affected patients as well as potential genetic confounders.

Given the results from this retrospective, exploratory study, larger prospective studies are now warranted. A novelty of our study was to include (although arbitrary) cutoffs for reproductive age; this should also be considered in future studies. Such future studies should investigate potential confounders related to long-term treatment in more detail, should include more male patients and the exact dates of menarche and menopause to determine the real "fertile age." Our study provides a strong rationale for future prospective studies exploring the effect of sex as well for the inclusion of respective subgroup analyses in future treatment trials in NMO/SD.

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