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Neuromyelitis Optica Spectrum Disorders in Africa

A Systematic Review

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Abstract

Background and Objectives

Neuromyelitis optica (NMO) is a CNS inflammatory disease that predominantly affects the optic nerves and the spinal cord. It is more frequent in Asian and African populations than in European ones. Data on epidemiology, clinical presentation, additional investigations, and treatment in the African continent are scarce. We aim to (1) collect and analyze published data on neuromyelitis optica spectrum disorder (NMOSD), (2) indicate challenges in the diagnosis and management, and (3) discuss opportunities for future research, education, and policy making, specifically on the African continent.

Methods

A systematic review was performed in January 2021 with the search terms "Neuromyelitis optica and Africa," "Devic Disease and Africa," and "NMOSD and Africa." We included all study types except case reports, correspondence, or conference abstracts on NMO or NMOSD. Extracted data included study design, country, study period, demographic and clinical characteristics, results of paraclinical investigations, and outcome. Data analysis was performed with descriptive statistics.

Results

We retrieved a total of 79 records, of which 19 were included. Ten of 54 African countries reported a total of 410 cases. Almost half of them were from North African countries. The mean age at diagnosis was 33 years (range 7–88 years), and 75% were female. Transverse myelitis followed by optic neuritis were the most frequent symptoms at the time of presentation. One hundred nineteen patients experienced at least 1 previous relapse, and 106 had a relapsing course after diagnosis. Relapses were treated with IV methylprednisolone. Azathioprine and steroids were used most often as maintenance treatments. Outcomes were rarely described.

Discussion

The majority of studies on NMOSD from the African continent are retrospective, and most countries do not report any data. Our systemic review shows that data derived from patients living in Africa correspond well to what has been previously published in meta-analyses on patients of African ancestry with NMOSD who live outside of Africa, except for a younger age at onset and a lower proportion of females. We advocate for systematic data collection to adequately capture and monitor the burden of NMOSD, for expansion of research efforts and facilities to perform fundamental and clinical research, and for improved access to health care including diagnostics, treatments, and rehabilitation services for people affected by NMOSD in the African continent.

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Glossary

EDSS = Expanded Disability Status Scale; **IPND** = International Panel for NMO Diagnosis; **IVMP** = IV methylprednisolone; **LETM** = longitudinally extensive transverse myelitis; **LMICs** = low- and middle-income countries; **MOG** = myelin oligodendrocyte glycoprotein; **MS** = multiple sclerosis; **NMO** = neuromyelitis optica; **NMOSD** = neuromyelitis optica spectrum disorder; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **TB** = tuberculosis; **TM** = transverse myelitis; **VEP** = visual evoked potential.

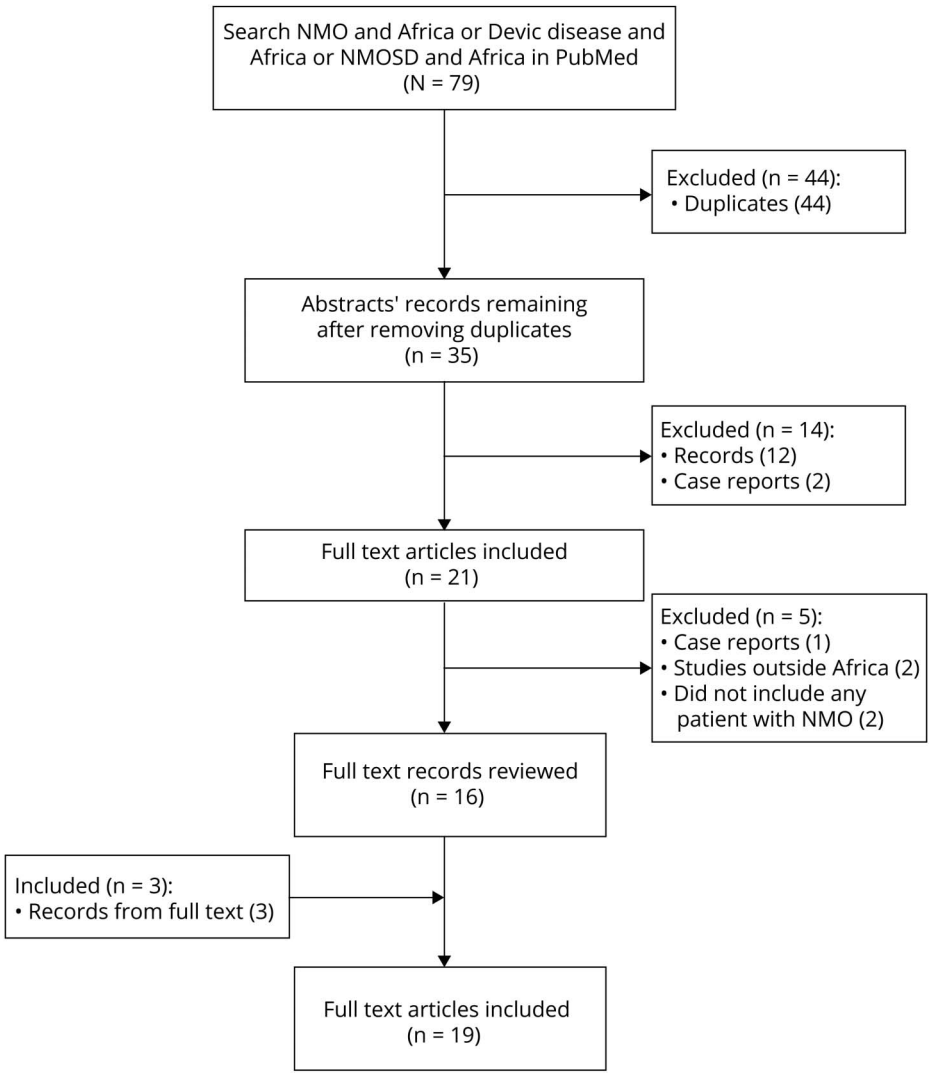
Neuromyelitis optica (NMO) is a CNS inflammatory disease that predominantly affects the optic nerves and the spinal cord.[1] NMO was first described in 1864 by Eugène Devic and has been regarded as a variant of multiple sclerosis (MS) until aquaporin 4 (AQP4) antibodies were discovered to be associated with some cases of NMO but not MS.[2-4] The correct diagnosis and distinction of these disorders from MS is important because treatment and prognosis are different.[5] Further clinical and fundamental research has led to the improved understanding of this condition as neuromyelitis optica spectrum disorders (NMOSDs) with variable clinical presentations in a disease spectrum rather than a single disease entity.[6] In a proportion of patients with AQP4-seronegative NMOSD, anti–myelin oligodendrocyte glycoprotein (MOG) antibodies are present.[7-10] The diagnostic criteria for NMO and disease spectrum have evolved over the years, and for an overview of these criteria, we refer to a review article on the evolving diagnostic criteria of NMO.[11] The most recent international consensus criteria have been defined by the International Panel for NMO diagnosis (IPND) in 2015.[6] NMOSDs have been found to predominantly occur in people from Asian or African descent as opposed to MS, which occurs primarily in populations from European ancestry.[12] In some studies performed on populations living off the African continent, NMOSD affected more persons of African descent, in comparison to non-Africans living in the same geographical setting.[12-14] This observation has been confirmed by a recent meta-analysis on the world-wide incidence and prevalence of NMOSD, leading to the conclusion that NMOSD was more frequent in people from Asian and African descent than in those from European descent.[15-17] However, only 1 report on NMOSD in the African continent from Nigeria was shortly mentioned in 1 of these reviews.[17] This is striking, as Africa is the continent harboring the largest population of people from Black origin, a race known to be most affected by NMOSD. Besides an estimate of prevalence in Ghana of 0.12/100,000 and South Africa of 5/100,000 coming from Multiple Sclerosis International Federation query data,[18] no data on prevalence of NMOSD in the African continent are available.

There have been a few studies that have investigated transverse myelitis (TM) in Africa as part of nontraumatic myelopathy,[19-28] with very few studies focusing on NMOSD.[21,29] Most of them focus on extrinsic compression and infectious diseases as important causes of myelopathy. In resource-limited areas, such as the low- and middle-income countries (LMICs) in Africa, it is not surprising that infectious diseases have been prioritized above noncommunicable diseases. Recent studies suggest that an increasing presence of noncompressive myelopathy occurs on the African continent.[21,30] The increasing prevalence of noncompressive myelopathy requires a comprehensive understanding of the other possible causes of myelopathy in the African continent. The African continent is predicted to be home to over half of the expected global population growth between 2015 and 2050,[31] highlighting the importance of addressing health and disease in the entire continent. The African Union, comprising all countries on the African continent, has published a document on the Health Strategy for the entire continent.[32] Hence, collecting data from the entire continent may allow evidence-based health care planning and resource allocation. We undertook this review of studies performed in Africa to describe the current knowledge on the epidemiology, clinical presentation, additional investigations, and treatment options available in patients affected by NMOSD on the African continent. The overall aim was to improve the understanding and consequences of this disease in Africa and suggest areas where further research is needed.

Methods

Two reviewers (A.K.M. and B.W.) independently performed a literature search on PubMed with the following search terms "Neuromyelitis optica and Africa," "Devic Disease and Africa," and "NMOSD and Africa," without filters on publication date, article type, or language. The search was performed between January 21 and 28, 2021. Both reviewers independently assessed the abstracts for eligibility according to the following inclusion criteria: (1) population described from the African continent, (2) topic of the article included NMO, NMOSD, or Devic disease, and (3) study design was a prospective or retrospective, case series, cohort studies, and cross-sectional studies. No specific diagnostic criteria for NMO(SD) were used for inclusion. We excluded studies based on the following criteria: (1) studies without African populations and studies describing patients from African ancestry in other countries, (2) case reports, (3) studies without participants with confirmed or suspected NMO, and (4) correspondence, conference abstracts, and commentaries due to limited data. Disagreements on eligibility were solved in consensus. Full-text articles were reviewed, and the reference lists were hand searched for identification of other relevant studies. We extracted the following data from the full-text articles: study characteristics (study design, study location and country, hospital (including type of hospital, teaching, or lower level), or community), demographic data, clinical variables including investigational findings of MRI, CSF, and results of AQP4 or MOG antibody tests, treatments, and outcomes. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Figure PRISMA Flow Diagram of the Study Selection Process



(PRISMA) guidelines for reporting systematic reviews were followed.[33] No systematic quality assessment of studies was performed. Descriptive statistics were used to analyze the data. The prevalence was estimated by calculating ratio of the total number of cases to the number of inhabitants per country (in the last year of the study period, most recent year was used in case there were multiple publications from a single country) and expressed as number of cases per 100,000 inhabitants. Population figures were derived from the United Nations.[34]

Data Availability

All data were derived from resources available in the public domain, as referred to in the reference list.

Results

Search Results

Our search terms provided us with a total of 79 records ("Neuromyelitis optica and Africa": 34 records, "Devic Disease and Africa": 35 records, and "NMOSD and Africa": 10 records). The selection process is depicted in the PRISMA flow diagram in the Figure. After removal of 44 duplicates, 35 records remained. We assessed the abstracts according to inclusion and exclusion criteria and remained with 16 records that were read full text. From these sources, 3 additional records were identified, leading to 19 records that were finally included.

Study Characteristics

Of 19 records in this review, 8 were from North Africa (4 countries—Morocco, Tunisia, Egypt, and Algeria), 4 from West Africa (3 countries—Senegal, Niger, and Nigeria), 5 from South Africa (all from South Africa), and 2 from East Africa (2 countries—Sudan and Ethiopia). Although all African regions are represented in the study sample, the data collected come from only 10 countries out of a total of 54 countries (18.5%) on the African continent. Almost all studies (95%) were retrospective, and 100% of the studies were hospital based. Publication dates varied between 1971

Table 1 Description of Study Characteristics

Number	Reference	Study period	Duration (yr)	Type of study	Sample size	NMO case sample size	Urban/ rural	Hospital/ community	Inpatients/ outpatients	Location	Country	Target population
1	47	2015–2018	3	Prospective case series	31	31	Urban	University Hospital	Inpatients	East Africa	Sudan	NMO
2	21	2010–2013	3	Retrospective cohort	105	4	Urban	University Hospital	Inpatients	East Africa	Ethiopia	Nontraumatic myelopathy (NMO/MS)
3	48	2004–2019	15	Retrospective case series	52	52	Urban	University Hospital	Inpatients	North Africa	Morocco	NMO
4	36	2015–2018	3	Prospective cohort	170	9	Urban	University Hospital	Inpatients	North Africa	Tunisia	CNS inflammatory disorders and opticospinal tract involvement–NMOSD
5	42,49[b]	1999–2015	16	Retrospective case series	64	64	Urban	University Hospital	Inpatients	North Africa	Morocco	NMOSD
6	37	2017–2018	1	Retrospective case series	400	20	Urban	University Hospital	Outpatients	North Africa	Egypt	CNS inflammatory diseases–NMOSD
7	39	2004–2015	11	Retrospective case control	42	21	Urban	University Hospital	Inpatients	North Africa	Algeria	ON/myelitis MOG-IgG and AQP4-IgG prevalence–NMOSD
8	38	1998–2014	16	Retrospective case series	938	8	Urban	University Hospital	Inpatients	North Africa	Algeria	CNS-demyelinating diseases–NMOSD
9	40	2011–2012	1	Retrospective case control	39	22	Urban	University Hospital	Outpatients	North Africa	Egypt	Suspected idiopathic inflammatory demyelinating CNS-NMOSD
10	45	2005–2016	11	Retrospective case series	29	29	Urban	University Hospital	Inpatients	South Africa	South Africa	NMO
11	44	1995–2011	16	Retrospective case control	14	14	Urban	University Hospital	Inpatients	South Africa	South Africa	NMO cases with GBS controls
12	29[a]	2010–2011	8 mo	Prospective cross-sectional	100	2	Urban	University Hospital	Inpatients	South Africa	South Africa	Nontraumatic myelopathy–NMO
13	50	1996–2000	4	Retrospective case series	8	8	Urban	University Hospital	Inpatients	South Africa	South Africa	Recurrent CNS-demyelinating disease based on MRI and CSF–NMO
14	46	1977–1987	10	Retrospective case series	8	6	Urban	University Hospital	Inpatients	South Africa	South Africa	Pulmonary TB and NMO, optic neuropathy, or myelopathy
15	51	2011–2018	7	Retrospective case series	16	16	Urban	University Hospital	Inpatients	West Africa	Senegal	NMOSD
16	41	1996–2017	21	Retrospective case series	7	4	Urban	University Hospital	Inpatients	West Africa	Niger	Demyelinating diseases–NMOSD
17	52[a]	2011–2014	3	Retrospective case series	5	5	Urban	University hospital	Inpatients	West Africa	Senegal	NMO
18	43[a]	1957–1969	12	Retrospective cohort	9,600	95	Urban	University Hospital	Inpatients	West Africa	Nigeria	All medical neurologic illness–NMO

Abbreviations: AQP4 = aquaporin 4; GBS = Guillain-Barré syndrome; MOG-IgG = myelin oligodendrocyte glycoprotein–immunoglobulin G; MS, multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis.
[a] These studies were included after hand searching the references of the full-text articles.
[b] 9 patients presented in one study[49] were included in the 64 patients analyzed by another study.[42]

and 2020, but 15/19 (79%) articles were published after 2004. The data collection period varied between 1 year and 21 years (Table 1). Many studies documented a diagnosis of NMOSD using the IPND 2015[6] diagnostic criteria in 9 of 19 records. Earlier diagnostic criteria were used in the remaining studies (1894 Devic NMO case—2/19, 1999 NMO criteria[35]—5/19, 2006 NMO criteria[1] 3/19) (Table 1 and Table 3). Other studies had diverse populations with patients with NMOSD included in 4/19 studies on demyelinating diseases of the CNS, 3/19 studies on general inflammatory conditions of the CNS, 2/19 studies on nontraumatic myelopathy, and 1/19 studies on all medical neurologic diseases (Table 1). The total number of patients diagnosed with NMO or NMOSD from 10/54 countries was 410. The majority of cases (48%, N = 196) have been described in North African cohorts, followed by West Africa (29%, N = 120) and South Africa (14%, N = 59), with the lowest number of reported cases (9%, N = 35) coming from East Africa (Table 2). The proportion of NMO cases increased from 2% in nontraumatic myelopathy (4/105 + 2/100 cases[21,29]), to 5% in cohorts of CNS inflammatory diseases (20/400[36] + 8/938[37] + 9/170 cases[38]), and to 58% in cohorts of patients presenting with ON and TM, in whom the clinical suspicion of NMOSD is high (22/39 + 21/42 + 4/7 cases).[39-41] However, definitions used to diagnose NMO/NMOSD varied between studies and differed according to the year of publication (Table 3). The time to diagnosis from onset of the symptoms ranged from weeks to years, with most studies stating a time to diagnosis of more than 9 months.

Demographic Characteristics

The NMO-to-MS ratio is lower in North African countries (9:67,[36] 64:503,[42] 20:330,[37] 8:877[38]) and higher in studied populations from sub-Saharan Africa (2:0[29], 4:3[41], 95:2[43]). Women are affected most frequently with NMO (82%, 252 women out of total of 309 patients from 16 studies excluding studies without complete data on NMO[21,29,43]). The mean age at diagnosis of NMO was 33 years, and the mean age by region was highest in East Africa (38 years), followed by North Africa (35 years), West Africa (34 years), and finally South Africa (29 years). In one study from Tunisia[36] the authors reported a significantly higher mean age of 51 years, quite different from all the other studies where the range was between 20 and 40 years. The age of those affected ranged from 7 to 88 years (Table 2). Prevalence estimates ranged between 0.004/100,000 in Ethiopia and 0.1/100,000 and 0.17/100,000 in Senegal and Nigeria, respectively (Table 4).

Clinical Presentation and Comorbidities

The clinical presentation was variable between the studies (Table 3). After excluding 4 studies without detailed clinical information,[21,29,40,43] the remaining 15 studies represented a sample size of 287 subjects. Among these, TM was the most common presenting syndrome (45%), followed by ON (41%), both TM and ON combined (15%), and finally brainstem syndromes (8%). One hundred eleven patients were evaluated and diagnosed after they had experienced a previous attack. One hundred six patients had at least 1 relapse during further follow-up. Seven studies described the presence of comorbid connective tissue diseases either by clinical or laboratory evidence of predominantly antinuclear antibody–related diseases. Some studies specifically investigated the presence of HIV and tuberculosis (TB) in the study population. No definite conclusions on the association of these concurrent infections, that are highly prevalent on the African continent, were drawn.[42,44-46]

MRI, Visual Evoked Potential, and Optical Coherence Tomography Data

Of the studies included, 16 studies reported detailed MRI data, providing a sample size of 309 participants of whom MRI characteristics were reported (Table 5). Brain lesions appeared in 51% (159/309), and longitudinally extensive transverse myelitis (LETM) was reported in 73% (225/309) of the patients. The region most affected in the spinal cord, based on 11 studies[36,37,41,42,44,47-52] in which detailed MRI results were reported by the spinal region (sample size of 223 participants), was the cervical cord (91/223, 41%). This was followed by the cervicothoracic cord (54/223, 24%) and finally the thoracic cord (25/223, 11%).[37,41,42,44,47,48,50-52] Visual evoked potentials (VEP) were abnormal in the majority of the patients in whom they were performed.[36,38,39,44,48,51,52] Optical coherence tomography was mentioned only in 1 study and was abnormal in a patient with recurrent ON.[38]

Laboratory Tests

Of the 12 studies that performed an AQP4 antibody assay, 53% (147/276) of cases were positive.[36-42,45,47,48,51] Most studies used indirect immunofluorescence cell-based assay (Table 5). MOG antibody assay was only reported in 2 studies from North Africa and was positive in 10% (7/73) of the patients.[39,48] Oligoclonal bands were present in only 5% (10/221) of patients in the 12 studies in which they were assessed.[36-42,45,47,50,52]

Treatment

The treatment modalities and outcomes are summarized in Table 6. Steroids and azathioprine were the most frequently used therapies. The main treatment modality for acute attacks was IV methylprednisolone (IVMP) for a duration of 3–5 days but in 1 study up to 10 days.[41] In 2 studies, oral prednisolone was used.[43] Another 2 studies did not present any information about their treatment modalities.[36,53] A few cases received treatment with plasmapheresis 3 to 6 sessions every other day in Morocco and Algeria (4%, 16/410) or IV immunoglobulins (less than 1%, 2/410). The maintenance therapy consisted of steroids (52%, 211/410), with a few cases treated with methotrexate (n = 2), mycophenolate mofetil (n = 3), cyclophosphamide (11%, 47/410, only Morocco), and mitoxantrone (n = 4). The second most used maintenance therapy was azathioprine, (28.3%, 116/410), and in a few cases, rituximab was used in Morocco (6.3%, 26/410). The treatments led to a favorable outcome in about 50% of the studies that reported treatment outcomes. However, clinical outcomes were described only in a few studies, and the

Table 2 Demographic Characteristics of Patients With Neuromyelitis Optica Spectrum Disorder in Africa

Number	Reference	Country	MS	Associated autoimmune diseases and infections	Others	NMO specific					
						Age yr	Range	Sex (F, n)	Sex F %	Time to diagnosis	HIV
1	47	Sudan				38	±12.8	25	81	X	
2	21	Ethiopia				X	X	X	X	19 mo	9
3	48	Morocco				33	7–55	34	65	9 mo	X
4	36	Tunisia	67	6 positive ANA, CIS = 29, Behcet disease = 2, sarcoidosis = 2, Sjögren = 1, vasculitis = 1, others 23, and non-classified 36		51	26–88	8	89	X	X
5	42,49	Morocco	503	15 patients (24.2%), Sjögren 5, ITP 3, Behcet 3, SLE 2, thyroid 5, and 5 developed TB		36	16–63	50	78	26 mo	X
6	37	Egypt	330	30 others, 2 rheumatoidarthritis, 2 hypothyroidism, 1 lupus, 1 myasthenia, 2 ANA positive, and 1 anti-dsDNA	50	34	15–59	17	85	80 mo	X
7	39	Algeria		ANA and anti-dsDNA in 2 patients, seronegative for AQP4 and MOG antibodies		33	19–58	14	67	X	X
8	38	Algeria	877	Anti-SSA antibodies 2 patients, anti-TPO = 1, and rheumatoid arthritis = 1	61	29	16–44	6	75	X	X
9	40	Egypt	17			29	+- 8.5	17	77	X	X
10	45	South Africa		HIV positive (1 HIV with ANF 1:2560 and positive anti-dsDNA), HIV negative (4 positive ANF, 2 anti-Ro, 1 anti-GAD, 1 anti-Ma2, nonclinical)		33	17–58	24	83	2 y in HIV positive and 14 y in HIV negative	12
11	44	South Africa		Pulmonary TB cases		26	18–41	11	79	X	6
12	29	South Africa		ADEM 4, idiopathic 4, and lupus 1		25	15–33	X	X	X	50
13	50	South Africa				32	8–42	6	75	X	X
14	46	South Africa		Pulmonary TB and NMO		25	15–33	4	67	X	X
15	51	Senegal				30	12–55	12	75	X	X
16	41	Niger	3			37	19–66	2	50	X	X
17	52	Senegal				34	18–50	3	60	X	X
18	43	Nigeria	2			X	X	X	X	X	X
						Mean = 33	Range 7–88				

Abbreviations: ADEM = acute disseminated encephalomyelitis; ANA = antinuclear antibody; ANF = antinuclear factor; anti-dsDNA = anti-double stranded DNA; anti-GAD = anti glutamic acid decarboxylase; anti-Ma2 = antibodies recognizing Ma2 protein; anti-SSA = anti–Sjögren's-syndrome-related antigen A; anti-TPO= anti thyroid peroxidase antibodies; AQP4=aquaporin 4; CIS = clinically isolated syndrome; ITP = idiopathic thrombocytopenic purpura; MOG = myelin oligodendrocyte glycoprotein; NMO = neuromyelitis optica; SLE = systemic lupus erythematosus; TB = tuberculosis.
The mean for female sex is 75%.
Others include idiopathic; non-classified was not further specified in the study. X means that the data were not reported in the study.

Expanded Disability Status Scale (EDSS) was reported in only 4 of them.[42,47-52]

Discussion

We have reviewed the epidemiology, clinical presentation, additional investigations, treatment options, and outcomes of patients with NMOSD on the African continent. We found only limited data available in the literature, with only 10 of the 54 countries reporting on patient cohorts, and most data were hospital based. NMOSD occurs in all regions of the continent, suggesting that it is a pan-African occurring disorder. Indeed, a number of case reports, including reports from countries not represented in our review, have been published (Burkina Faso, Ghana, South Africa, Uganda, Nigeria, and

Table 3 Clinical Characteristics of Patients Presenting With NMOSD in Africa

Author	Location by region	Country of data source	NMO/NMOSD criteria	NMO cases (n)	TM %	ON %	Both TM and ON %	Brain stem %	Multifocal (all 3) %	Relapse %
47[a]	East Africa	Sudan	2006	31	68	32				100
21[d]	East Africa	Ethiopia	1999	4	X	X	X	X	X	X
48[b]	North Africa	Morocco	2006, 2015	52	73	94	0	19		X
36	North Africa	Tunisia	2015	9	56	11	33	0	0	100
42,49	North Africa	Morocco	2015	64	27	38	0	11	23	86
37	North Africa	Egypt	2015	20	35	40	0	25		100
39	North Africa	Algeria	2006, 2007, 2015	21[f]	62	38	0			76
38	North Africa	Algeria	2015	8	25	13	50		13	88
40[d]	North Africa	Egypt	2006	22	X	X	X	X	X	100
45[c]	South Africa	South Africa	1999	29	55	41	0			41
44	South Africa	South Africa	1999	14	0	0	100			100
29,[d]	South Africa	South Africa	1999	2	X	X	X	X	X	X
50	South Africa	South Africa	1999	8	50	38	0	13	0	100
46	South Africa	South Africa	1894	6	0	0	100			100
51	West Africa	Senegal	2015	16	31	6	63			50
41	West Africa	Niger	2015	4	50	0	50			50
52,[e]	West Africa	Senegal	2006	5	0	0	100			60
43,[e,d]	West Africa	Nigeria	1894	95	X	X	X	X	X	X
				410						

Abbreviations: NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis; TM = transverse myelitis.
[a] There was optic atrophy in 22 patients in whom fundoscopy was performed, and 8 of the 10 patients with optic neuritis were blind.
[b] The symptoms were not segregated into distinct items.
[c] 5/12 in HIV positive and 11/17 presented with myelitis, 6/12 HIV positive and 6/17 in HIV negative presented with ON, and 6 HIV positive and 6 HIV negative relapsed.
[d] Excluded studies that did not have complete data on clinical presentation. For the studies that had patients presenting with 100% both TM and ON, Silber et al.[46] report that the symptoms of ON preceded those of TM in 4 patients by a mean of 33 days, whereas Zatijura et al.[44] reported that TM and ON appeared simultaneously in 2 cases, while TM preceded ON by 3 days to 2 months or followed ON by between 2 days to 2 months.
[e] Dadah et al.[52] also reported that that ON preceded TM by a year, whereas in another patient, ON followed TM within a month.
[f] 21 NMO patients according to 2007 criteria, 6 according to 2006 criteria, 13 according to 2015 criteria.

Togo).[46,54-60,e1-e6] Prospective data are scarce, and most studies were retrospective in nature, with inclusion criteria that varied over time in accordance with evolving diagnostic criteria of NMO and NMOSD.[11]

Two recent reviews have emphasized the high prevalence of NMOSD in populations of African ancestry that may be as high as 10/100,000 in black people.[15,e7,e8] All studies cited in these reviews have been performed off the African Continent in French Martinique, the United States, the United Kingdom, Cuba, and New Zealand. The exact incidence and prevalence of NMOSD on the African continent remain unknown to date. The prevalence estimates that resulted from the analysis of the collected data from the published literature likely represent a massive underestimation of the real prevalence. Indeed, the estimated prevalence data from South Africa are lower than those reported in the query data from Multiple Sclerosis International Federation.[18] This underscores the need for prospective nationwide or even continent-wide data collection initiatives. Limited human and financial resources, lack of systematic data collection on neurologic disorders, and numerous barriers to health care services may contribute to the lack of knowledge on epidemiologic data on NMOSD in Africa.[e9]

NMOSD predominantly affects women and young adults in Africa, similar to other parts of the world. However, the female-to-male ratio of 3.5:1 is lower than reported in other review articles, which may be as high as 9:1 in AQP4-IgG–positive NMOSD.[e7] The age at diagnosis in our review was younger than the average of 40 years stated in other reviews.[15,e7,e8] In comparison to a study that evaluated racial differences, Afro-Americans and Afro-Europeans had a younger age of onset than patients of European descent,[e10] which may mean that the African ancestry may predispose to a younger age at onset. Sex, however, did not differ between

Table 4 Prevalence Estimates

Country	Prevalence estimate (N/100,000 inhabitants)
Algeria	0.053
Egypt	0.020
Ethiopia	0.004
Morocco	0.14
Niger	0.025
Nigeria	0.17
Senegal	0.10
South Africa	0.052
Sudan	0.074
Tunisia	0.078

races in this study, and between 84% and 90% were females.[e10] Especially in African countries, the early age of onset and more severe disease course may have a high impact, as comprehensive rehabilitation services are inequitable and inaccessible in Africa.[e11] Older patients may not come to the attention of health care services, and the average life expectancy of 62 years for men (range 54–72 years) and 65 years for women (range 59–75 years) may be another explanation for the young age at onset in our review.[e12] Women in Africa may be less likely to have access and attend to the hospitals[e13] in comparison to men, which may explain the higher proportion of men in our study. However, this hypothesis needs to be validated by community-based studies.

There seems a delay in the diagnosis as most of the studies identified patients after they had relapsed, which may translate into worse outcomes. Others reported that the median time to first relapse was about 5 months,[e14] which would mean that most of African patients are diagnosed only after a first relapse, as demonstrated in 8/19 of the studies.[36-39,47,49-51] This calls for early and accurate diagnosis with adequate relapse treatment and institution of a maintenance therapy to prevent subsequent relapses and disability. Indeed, it is well known that more relapses before and after treatment are independent predictors of severe motor disability.[e10] Outcomes were only rarely reported with variable measures, including general terms, modified Rankin Scale score, or EDSS score. The data collected in our review were insufficient to describe outcomes in patients reliably.

The NMO:MS ratio increases when moving from the northern parts of Africa toward the south. This is not unexpected as it is known that the prevalence of MS increases with increasing latitude and lower levels of vitamin D.[e15,e16]

The co-occurrence of HIV infection with NMOSD has been rarely described. However, the disease course does not differ from HIV-negative patients with NMOSD.[e17] Causality has not been proven yet, and potential pathophysiologic mechanisms need further investigation. Conflicting evidence exists also for TB and NMOSD.[e18-e20] A strong association of NMOSD with other autoimmune diseases, especially SLE and Sjogren syndrome, is well known and has also been found in some of the studies reviewed here.[e21-e23]

NMOSD can present with several clinical syndromes, which include TM, ON, and area postrema syndrome.[6,e24-e26] In our review, TM and ON were the most frequent presenting symptoms, whereas a combined opticospinal presentation and brainstem symptoms were less frequent. Whether other presentations occur less or are merely underreported in the African population is unknown and an area open to further research.

Most studies in our review have been published recently and used established diagnostic criteria with additional investigations including at least an MRI and serology.[6] There was a high frequency of LETM on spinal cord MRI and atypical MS-like brain lesions in most of these studies.[1,e27-e29] AQP4-IgG seropositivity was around 55%, which is slightly lower than has been reported in other studies,[e30-e32] probably due to the various inclusion criteria and assays used.[e33,e34] VEPs in NMO are useful in longitudinal follow-up of patients with NMO.[e35,e36] The frequency of an abnormal VEP was high in our review, which may be due to late presentation with residual deficits from previous relapses.

Relapse treatment in NMOSD consists of high-dose IVMP and/or plasmapheresis.[e37,e38] The latter is not readily available in most African countries and therefore hardly ever used according to our review in contrast to high-dose IVMP. Maintenance or preventive treatment recommendations for NMOSD include rituximab and mycophenolate as first-line agents, which are both not readily available in most African countries. Second-line agents include azathioprine, methotrexate, ciclosporin, mitoxantrone, and cyclophosphamide.[e37,e38] The most common preventive treatments used were steroids and azathioprine.

Both severe and mild cases may be missed, as many patients do not receive medical care in many parts of Africa. Both access to health care and universal health coverage are strikingly low compared to Europe and the United States and worst in sub-Saharan Africa.[e39,e40] Although the WHO recommends a ratio of 1 neurologist per 100,000 inhabitants, there is only a median number of 0.043 neurologist per 100,000 inhabitants in the WHO African region.[e41] Most of them (97%) practice in the capital city, and only 3% are based in rural areas.[e41] Some African countries have no neurologists at all.[e42] This problem starts at the level of (post)graduate education, with limited options for neurologic training and scarce neurologic faculty available for teaching.[e43] Moreover, access to MRI, which is crucial in making a correct diagnosis, is not available in many regions of Africa. Although there has been an increase in availability of MRI in the past few years on the African continent, in West sub-Saharan Africa, there is still a very

Table 5 Results of Paraclinical Investigations in Patients Presenting With Neuromyelitis Optica Spectrum Disorder in Africa

			MRI lesions												
Author	**Country**	**NMO-specific sample size**	**Brain lesion %**	**Spine LETM %**	**Brainstem lesion %**	**Cervical lesion %**	**Thoracic lesion %**	**Cervical thoracic lesion %**	**MRI bulbar cervical**	**Whole spine**	**VEP abnormal**	**OCB present**	**AQP4 antibody (% positive in NMO sample size)**	**AQP4 antibody assay type**	**MOG antibody (% positive)**
47[a]	Sudan	31	26	94	0	94	0	0	0	0	0	6.5	74	ELISA	x
21	Ethiopia	4	x	x	x	x	x	x	x	x	x	x	x	x	x
48[b]	Morocco	52	71	60	0	37	10	19	0	0	94	x	38	x	8
36[c]	Tunisia	9	33	89	0	33	44	11	0	0	67	22	78	Indirect immunofluorescence on transfected cells (Eurimmun)	x
42, 49[d]	Morocco	64	83	70	0	30	13	44	0	3	0	9	47	Transfected fixed cell-based assay	n.d.
37[e]	Egypt	20	60	60	0	15	5	30	10	0	x	0	50	ELISA	x
39 [f]	Algeria	21	12.5%[f]	66.7%[f]	0	x	x	x	x	x	10	0	29	Commercial fixed cell-based assay (Eurimmun) or live cell-based assay (Austria or France)	14
38[g]	Algeria	8	25	88	0	x	x	x	x	x	13	0	38	x	x
40[h]	Egypt	22	41	73	x	x	x	x	x	x	x	x	95	ELISA	x
45[i]	South Africa	29	59	72	21%	x	x	x	x	x	x	m.d.	52	Commercial fixed cell-based assay (Eurimmun)	n.d.
44[j]	South Africa	14	43	71	0	21	7	14	0	7	x	x	x	x	x
29	South Africa	2	x	x	x	x	x	x	x	x	x	x	x	x	x
50	South Africa	8	100	100	0	50	25	25	0	0	x	0	x	x	x
46[k]	South Africa	6	0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	x	n.d.
51	Senegal	16	13	100	0	38	25	13	19	0	50	x	63	Indirect immunofluorescence on transfected cells	x
41[l]	Niger	4	0	100	25	50	0	25	0	0	0	0	50	x	n.d.
52	Senegal	5	0	100	0	60	0	40	0	0	100	x	x	x	x
43	Nigeria	95	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: AQP 4 = aquaporin 4; ELISA = enzyme linked immunosorbent assay; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis; m.d. = missing data; MOG = myelin oligodendrocyte glycoprotein; n.d. = not done; NMO = neuromyelitis optica; OCB = oligoclonal bands; VEP = visual evoked potential x = not reported; 0 = not done.
[a] Spinal cord MRI was normal in 2 patients.
[b] Anti-AQP4 antibodies were tested in only 57.7%, positive in 38.4% (20/30 patients) and anti-MOG antibodies positive in 40% (4/10 AQP4 seronegative patients). White matter hyperintensities in 37/52 patients, in 5/52 patients (10%) diencephalic lesions on brain MRI. Spinal cord MRI was normal in 1 patient.
[c] Anti-AQP4 antibodies were tested in 170 patients with inflammatory neurologic conditions. Brain MRI abnormalities were nonspecific lesions.
[d] Included spinal cord MRI with less than 2 affected segments in 14 patients, 47.6% of a total of 34 tested patients were positive for anti-AQP4 antibodies.
[e] Spinal cord MRI results were available in 19 patients. OCBs were done in only 2 patients and were negative.
[f] 21 patients had NMO according to 2007 criteria; MRI data reported only for 9 AQP4 and MOG positive patients; in 1 MOG positive patient, asymptomatic ADEM like lesions were present (1/8 patients with brain MRI), in all 3 patients longitudinal extensive optic neuritis (LEON) was present on orbit or brain MRI; in 1 MOG positive patient asymptomatic LETM was seen on MRI of the spinal cord; 5 AQP4 positive patients had LETM on MRI and 1 AQP4 positive patient had LEON (6/9 spinal cord LETM); VEP was only done in 2 AQP4 positive patients (1 symptomatic, 1 asymptomatic) and was abnormal in both of them.
[g] Spinal cord MRI was normal in one patient and showed spinal cord atrophy in another patient.
[h] AQP4 antibodies were tested in 39 patients with idiopathic neuroinflammatory diseases.
[i] In 5 patients brain MRI was not done. Brain MRI was abnormal in 7/10 HIV positive patients and in 10/14 HIV negative patients. Brain MRI showed tumefactive incomplete ring-enhancing lesions in 3/10 HIV positive patients; in 6/14 HIV negative patients a medullary hyperintensity was seen; in 10 patients abnormalities were periventricular or aspecific. OCB were not analyzed in 13 patients and negative in 16 patients.
[j] Brain MRI was not done in 4 patients and spinal cord MRI was not done in 5 patients. OCB were not reported, but in 2 patients an increased IgG index was recorded.
[k] MRI was done in only 2 patients (normal results). The rest were investigated with CT myelogram.
[l] VEP were reported in only 1 patient presenting with myelitis and were normal.

low number of facilities (0.30–0.48/million inhabitants,[e44]) compared with Europe or the United States (4.91–40 per million in 2019,[e45]). No access to AQP4 or MOG antibody tests has been reported by approximately half (48%, 13/27) of African and Eastern Mediterranean countries.[e46] This study also highlighted that patients with NMO in LMICs cannot afford immunomodulatory treatment, despite local availability of the treatments.[e46] The same problem likely applies to the diagnostic tests and facilities: despite improving availability, they may remain unaffordable for many patients. International and political efforts are ongoing to improve health care coverage in LMICs, like on the African continent (e.g., UHC2030—accelerating progress toward Universal Health Coverage).

Because of limited resources, applicability of the 2015 IPND NMOSD criteria in the African setting remains challenging. Furthermore, possible relations between HIV, TB, and NMOSD need further research, and as these diseases are highly prevalent and incident on the African continent, this could lead to novel insights. Immunogenetic studies could aid in confirming or finding new genetic risk factors, such as HLA associations in the African population. In Afro-Caribbeans, an association with HLA class II allele DRB1 03 has been reported before.[e47] Efforts toward development of a global neuroscientific community such as TreND in Africa[e48] may help to build educational and scientific capacity.

We have to address several limitations of our systematic review: most included studies were retrospective, provided incomplete data, described different populations, and used different NMO criteria over time. We also acknowledge the differences in race, genetic background,[e49] cultures, and access to medical care on the vast geographical African continent. Research on risk factors and outcomes in LMICs may benefit from these variability and lead to optimization of the diagnostic and treatment pathway taking into account the limited resources. All these aspects may affect the quality of the data in a significant way. However, a major strength of our review is that it captures all available data on NMOSD, excluding single case reports, from the literature from the African continent.

Clearly, prospective data registries from the African continent would help to solve some issues raised in this article. Initiatives such as NMOBase and MOGBase, both as part of the MSBase international registry, may serve as easy-to-use data collection platforms. This registry is an international collaboration dedicated to sharing, documenting, and evaluating outcomes data in MS and other neuroimmunologic diseases, including NMO and MOG. The only 2 African countries currently actively participating in MSBase are Egypt and Tunisia. Efforts to increase awareness and knowledge on NMOSD in Africa have included dedicated conferences and support to perform AQP4 antibody assays, in which The Guthy-Jackson Charitable Foundation has played an important role. The CIRCLES initiative is collecting biospecimens

Table 6 Treatment Options and Outcomes Among Patients Presenting With NMOSD in Africa

Author	Country	NMO sample size	Acute treatment by %				Maintenance treatments by %							Outcomes
			IVMP	Pred	TPE	IVIG	Pred	AZA	MTX	MMF	CP	Mitoxantrone	RTX	
47	Sudan	31	84				84	68						Complete improvement in 2, improvement with disability 22, and no improvement 7; 28 EDSS score 7.5 or higher; 3 EDSS score 5 or lower at entry
21	Ethiopia	4		100										
48	Morocco	52	69		25			10			6		46	20 favorable and stable in 26 patients worsened in 5 patients
36	Tunisia	9												EDSS score at entry 6
42,49	Morocco	64	73		3	3	100	25		3	67	5	3	EDSS score at entry 4.4 and EDSS score at exit 5.1
37	Egypt	20	100				100	40	10	5	5			EDSS score at entry 4.6
39	Algeria	21	100		5		100	5						
38	Algeria	8	100				0	0						
40	Egypt	22	100				100	100				5		EDSS score at entry 4.0
45	South Africa	29	100				100	100				0		
44	South Africa	14	x	x	x	x	x	x	x	x	x	x	x	
29	South Africa	2	x	x	x	x	x	x	x	x	x	x	x	
50	South Africa	8	100				100							Favorable in 5 patients
46	South Africa	6	50	50			0							
51	Senegal	16	25	75			100	63						Favorable in 10 patients (mRS score = 2), 2 died, and 4 lost to follow-up
41	Niger	4	100					100						
52	Senegal	5	20	80			100	0						Favorable in 1 patient, stable in 3 patients, and deteriorated in 1 patient
43	Nigeria	95		Yes			0	0						
Total		410												

Abbreviations: AZA = azathioprine; CP = cyclophosphamide; EDSS = Expanded Disability Status Scale; IVIG = IV immunoglobulin; IVMP = IV methylprednisolone; MMF = mycophenolate mofetil; mRS = modified Rankin Scale; MTX = methotrexate; NMO = neuromyelitis optica; PRED = prednisone or prednisolone, oral corticosteroids; RTX = rituximab; TPE = therapeutic plasma exchange or plasmapheresis; x = not reported in the paper.

and clinical data, currently only in North American sites, including the United States and Canada.[e50] An NMOSD African network could be envisaged in the future. The recently inaugurated African Stroke Organization may serve as an example to establish within Africa collaborations and to strengthen the African continent on its mission to reduce the burden of neurologic diseases.

There is a clear need for prospective data collection on NMOSD in the African continent to assess the real prevalence, incidence, and burden of this disease, which may turn out not to be ultra-rare in this continent at all (ultra-rare disease affects <1 per 50,000 persons). The lower proportion of women and younger age at onset need further investigation. Without increasing the number of neurologists per capita, educating the population, improving accessibility and affordability of diagnostics (AQP4 and MOG antibody tests and MRI) and acute and preventive treatments, cases will continue to be missed, patients will remain undertreated and their functional outcomes will not improve. We hope that our article serves as a call to action to direct research efforts and resources toward NMOSD in Africa, as the knowledge we gain in this way may benefit all people affected by NMOSD throughout the world.

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Appendix Authors

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Judith Derdelinckx, MD, PhD	University of Antwerp, Wilrijk, Belgium	Interpreted the data and revised the manuscript for intellectual content
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