Mortality in neuromyelitis optica is strongly associated with African ancestry

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Background

Neuromyelitis optica spectrum disorder (NMOSD) is a severe autoimmune disease of the optic nerve, spinal cord, and, less frequently, brain.[1] Severity and degree of recovery from relapses are the factors that determine long-term visual and motor disability and mortality.[1] Mortality rates in NMOSD worldwide range from 9% to 32%, depending on age, relapse rate, and recovery from attacks.[2,3] In examining mortality data from 2 large, ethnically diverse NMOSD Centers in the Mid-Atlantic United States, we observed a striking race distribution: most deceased patients were of African ancestry. In this analysis, we focus on race as a risk factor for mortality in NMOSD.

Methods

This is a retrospective study of all patients with NMOSD seen at 2 large US-based clinics: Johns Hopkins Hospital (Baltimore, MD) and New York University (New York, NY). NMOSD was defined by the 2015 International Panel of NMO Diagnosis.[4] Race was patient reported, whereas all other clinical and demographic factors, including the cause of death, were confirmed by site investigators. Patients not seen in the previous 12 months were called to verify living status. Time to diagnosis, frequency of clinic/hospital visits, and treatment regimen for relapses acted as surrogates of health care access. Institutional review boards from both institutions approved this study.

Results

A total of 427 NMOSD patients were included in this analysis, 328 from Johns Hopkins Hospital and 99 from New York University. In total, 30 patients died during follow-up (table), with an annual mortality rate of 0.68 deaths per 100 patient-years. The mean disease duration at time of death was 6.9 years. Patients of African ancestry constituted 41% of our clinic population, but they comprised 90% of the deceased NMOSD patients, with average age at death of 52.3 years. The other 3 deceased patients included an Asian woman aged 85 years, a Caucasian man aged 69 years, and a Caucasian woman aged 65 years. The overall mortality rate in our total cohort was 7.0%, and among those of African ancestry was 15.4% ($p < 0.0001$).

Patients in each race group were similar regarding age, sex, aquaporin-4 serostatus, time to diagnosis, acute treatment care, and access to our clinics (table). Although more deceased patients were untreated at final follow-up (22% vs. 4%), there was no difference in treatment rates among the races.

Table Demographic and clinical characteristics of cohorts

Characteristic	Deceased cohort only			Total NMOSD cohort				
	African ancestry	Caucasian ancestry	Other	African ancestry	Caucasian ancestry	Hispanic ancestry	Asian ancestry	Total
No. of patients	27	2	1	175	198	35	19	427
Female sex (%)	21 (78)	1 (50)	1 (100)	156 (89)	163 (82)	29 (83)	19 (100)	367 (86)
Proximity to clinic (%), within mid-Atlantic	27 (100)	1 (50)	1 (100)	164 (94)	147 (74)	32 (91)	16 (84)	359 (84)
AQP4 seropositive, (%)	23 (85)	1 (50)	1 (100)	155 (89)	144 (73)	25 (71)	16 (84)	340 (80)
Age at disease onset in y, mean (SD)	43.1 (15.0)	60.2 (3.1)	78.0	37.1 (15.8)	42.6 (17.1)	35.4 (19.5)	46.0 (16.0)	39.9 (16.7)
Duration of disease in y, mean (SD)	7.0 (5.0)	6.6 (0.1)	7.0	10.6 (8.1)	10.2 (7.3)	10.0 (6.9)	11.2 (7.9)	10.4 (7.7)
Delay in diagnosis	4.0 (4.7)	0.1 (0)	1.0	4.0 (6.0)	4.3 (7.0)	3.6 (4.6)	3.7 (4.4)	4.1 (6.3)
Preventive medication at final follow-up (%)								
Azathioprine	4 (15)	0 (0)	0 (0)	12 (7)	15 (8)	6 (17)	1 (5)	34 (8)
Rituximab	9 (33)	1 (50)	0 (0)	94 (54)	117 (59)	19 (54)	11 (58)	241 (56)
Mycophenolate mofetil	6 (22)	1 (50)	1 (100)	52 (30)	54 (27)	5 (14)	5 (26)	116 (27)
Other	2 (7)	0 (0)	0 (0)	9 (5)	8 (4)	3 (9)	1 (5)	21 (5)
None	6 (22)	0 (0)	0 (0)	8 (4)	4 (2)	2 (6)	1 (5)	15 (4)
Received PLEX for the last relapse, (%)	22 (81)	2 (100)	0 (0)	N/A[a]				
NMOSD relapse within 1 y before death (%)	22 (81)	1 (50)	0 (0)	N/A				
High cervical/brainstem (%)	20 (74)	1(50)	0 (0)					
Age at death in y, mean (SD)	50.1 (14.8)	66.8 (3.0)	85.0	N/A				
Cause of death (%)				N/A				
Complications of NMOSD	19 (70)	2 (100)	1 (100)					
Cancer	4 (15)	0 (0)	0 (0)					
Liver failure	1 (4)	0 (0)	0 (0)					
Renal failure	1 (4)	0 (0)	0 (0)					
Advanced AIDS	1 (4)	0 (0)	0 (0)					
Suicide	1 (4)	0 (0)	0 (0)					
Comorbidities, excluding cause of death (%)				N/A				
High blood pressure	8 (30)	1 (50)	1 (100)					
Diabetes	7 (26)	1 (50)	1 (100)					
Other autoimmune disease	4 (15)	0 (0)	1 (100)					
Mood disorder	4 (15)	0 (0)	0 (0)					

Continued

Table Demographic and clinical characteristics of cohorts *(continued)*

Characteristic	Deceased cohort only			Total NMOSD cohort				
	African ancestry	Caucasian ancestry	Other	African ancestry	Caucasian ancestry	Hispanic ancestry	Asian ancestry	Total
Asthma	3 (11)	0 (0)	0 (0)					
Renal insufficiency	3 (11)	0 (0)	0 (0)					
Thyroid disease	3 (11)	0 (0)	0 (0)					
Hyperlipidemia	2 (7)	0 (0)	0 (0)					
Cancer	1 (3)	1 (50)	0 (0)					

Abbreviations: AQP4 = aquaporin-4; NMOSD = neuromyelitis optica spectrum disorder; PLEX = plasma exchange.
[a] Previously published data in NMOSD reported that approximately 20%–78% of patients are escalated to plasma exchange.[12]

In 22 of 30 deceased patients (73%), cause of death was related to NMOSD (table). Most deaths, 70%, were preceded by a relapse in the brainstem and/or upper cervical spinal cord within the previous 12 months despite preventive medications in 80% of patients at the time of the fatal relapse.

Discussion

Our study involved a very large patient sample—427 patients from 2 large specialized NMO centers. The overall mortality rate was 7.0% (30 of 427 patients). This rate is slightly lower than in contemporary studies (9%–13%)[3,5] and considerably improved from older landmark studies (22%–32%).[2,6,7] The decrease in mortality over time is likely due to earlier diagnosis, use of plasmapheresis for acute relapses, and preventive immunotherapies, which have been shown to decrease relapse rates in observational studies.[8] It is important that the definition of NMOSD has changed over the past 2 decades, allowing for milder cases to be diagnosed. Thus, the decrease in mortality could also be in part a technical artifact ("Will Rogers effect").

The most striking finding of this study is the observation that nearly all the deceased patients in our combined cohort were of African ancestry. Patients of African ancestry make up 41% of the total cohort, but account for 90% of the mortality. This is unlikely due to chance ($p < 0.0001$, Fisher test) or to differences in delay in diagnosis, clinic access, or treatment (table). This is also unlikely to be due to differences in death rates among races: according the CDC, mortality rate among those of African race was 0.8% and 0.7% among Caucasians (2009–2014). One other study has identified African ancestry as a strong predictor of mortality in NMOSD. In Brazil, where the estimated mortality rate among all patients with NMOSD is 23%, the mortality rate among Afro-Brazilians is a staggering 58%.[9] Two European studies did not implicate African race as a risk factor for mortality, but the proportion of African patients in their cohorts was much lower than in the Eastern US and Brazilian NMOSD cohorts.[2,10,11] Our results have

important implications for management of patients of African ancestry with NMOSD. Further studies, especially prospective studies assessing factors that affect the severity of relapses, may shed light on the high risk of death among patients of African ancestry with NMOSD.

Disclosure

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