RESPONSE TO DISEASE MODIFYING THERAPIES IN AFRICAN AMERICANS WITH MULTIPLE SCLEROSIS

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Background: The African American (AA) population has a lower risk for developing multiple sclerosis (MS) than Caucasian (CA) population; however, the disease tends to be more severe with early disability in AA. The reason underlying the discrepancy in disease severity is not yet understood, and it could be caused by different response to disease modifying therapies (DMTs).

Objective: To evaluate whether there are significant differences in profile of response to disease modifying therapies related to ethnicity, while controlling for disease characteristics.

Design: We performed a retrospective chart analysis of MS patients undergoing treatment with DMTs. Rating of disease progression was based on expanded disability status score (EDSS) difference at the time of first and last visit.

Patients: AA and CA patients with MS.

Results: Sex and age at the time of diagnosis did not differ significantly between AA and CA. There was statistically significant difference in disease duration, which was longer among CA patients ($P<.001$). Median of EDSS difference was higher in AA population than in CA population ($P<.001$). Increased EDSS difference suggests poorer response to DMTs among AA patients in our study.

Conclusions: AA patients showed poorer response to DMTs when compared with CA patients. This suggests a trend, however, further prospective studies on the response of AA patients to DMTs are warranted. (*Ethn Dis*. 2012;22(2):221–225)

Key Words: African American, Response, Disease-Modifying Therapy, Difference

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INTRODUCTION

The African American (AA) population has a lower risk for developing multiple sclerosis (MS) compared to the Caucasian (CA) population[1–4]; however, the disease tends to be more severe. Available data from multiple studies suggest that AA ethnicity is a risk factor for having a more disabling disease course[2] as well as developing opticospinal MS and transverse myelitis more frequently.[1] AA patients are also at greater risk for requiring a cane to ambulate and for developing wheelchair dependency earlier than CA patients.[1] Increased activity of humoral immune response with higher IgG index and synthesis rate of IgG in CSF of AA patients was also found.[5] This finding extends interethnic clinical differences in MS to immune response itself.

To our knowledge, there are little data available about response to treatment with disease modifying therapies (DMTs) in the AA population. This is mainly due to small sample sizes to establish statistical significance. Based on our own clinical experience, we hypothesize that response of the AA population in South Carolina to currently used DMTs is poorer when compared with the CA population. Our hypothesis is also based on available data from post hoc analysis of Evidence of Interferon Dose Response: European North American Comparative Efficacy (EVIDENCE) data set that suggested a nationwide trend of lesser response in AA patients.[6]

The purpose of our study was to compare the response to currently used DMTs in AA and CA patients in South Carolina based on clinical progression of the disease as measured by the expanded disability status score (EDSS) and try to replicate the above mentioned trend. Further knowledge about responding to widely used DMTs could help better target treatment for this population and affect the disability.

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PATIENTS AND METHODS

A list of patients diagnosed with MS and treated at the Medical University of South Carolina (MUSC) was generated based on billing code 340.0. The MUSC is a tertiary care center and as such provides medical care to a wide range of patients from South Carolina. Patients with MS were referred by primary care physicians, private neurologists or were previously hospitalized at MUSC and diagnosed with MS.

Medical records from January 1985 until October 2010 were reviewed for all self-defined AA and CA patients with MS. To meet inclusion criteria, patients had to be diagnosed with relapsing-remitting or secondary progressive MS and be treated with currently used DMTs for the entire disease course. First and last visit had to be at least one

year apart. At the time of their first visit patients were either already diagnosed with MS and treated by different practitioners or newly diagnosed at MUSC and treatment naive.

Sixty-six of 90 AA patients were eligible for the study. A comparison group consisted of 67 randomly selected CA patients with similar follow-up characteristics. Retrospective chart analysis of AA and CA MS patients was performed and data including race, sex, age, disease duration and treatment agents were extracted. Chart review and data extraction was not blinded to ethnicity.

Rating of disease progression was based on the EDSS difference between the last and first visit. If the EDSS score was not recorded in the chart, the investigator did a post hoc EDSS rating. If last visit was recorded during an active relapse, then a previous visit was used for EDSS calculation. We chose the EDSS as one of the most widely utilized assessment instruments in multiple sclerosis and standardized measure of global neurological impairment in MS.

Since sex is an important confounding factor affecting disease severity and disability, we also performed subgroup analysis and compared EDSS differences between CA and AA males and females.

Patients with primary progressive disease and Devic's disease were excluded from the study. Patients who were not treated consistently or treated with agents different than conventionally used DMTs (AVONEX®, Rebif®, BETASERON®, COPAXONE® and TYSABRI) were also excluded from the study.

Differences between groups were assessed using the chi-square test for gender; two-sided *t* tests for age variables and the Mann-Whitney U (nonparametric) test for EDSS scores change and subgroup gender analysis.

RESULTS

The initial participant list was generated based on diagnostic code 340.00 and identified approximately 100 AA patients diagnosed with MS. Following inclusion criteria, 66 AA patients were eligible for our study. As a comparison group, we used a randomly selected group of 67 CA patients with similar features. We performed a retrospective chart analysis and extracted data including race, sex, age, disease duration and treatment agent. Investigator assigned EDSS scores at first and last follows up and progression of the disease were expressed as a difference between scores at first and last visit.

Basic characteristics of both groups were very similar: 13.6% of AA patients and 20.9% of CA patients were men ($P=.36$). Mean age at the time of diagnosis was 34.3 for AA patients and 36.9 for CA patients ($P=.13$). Based on treatment agent profile, 66% of AA patients were treated with interferons, 16% were treated with glatiramer acetate and 13% received treatment with natalizumab. In the comparison group, 61% of CA patients were treated with interferons, 25% received glatiramer acetate and 13% patients were on natalizumab.

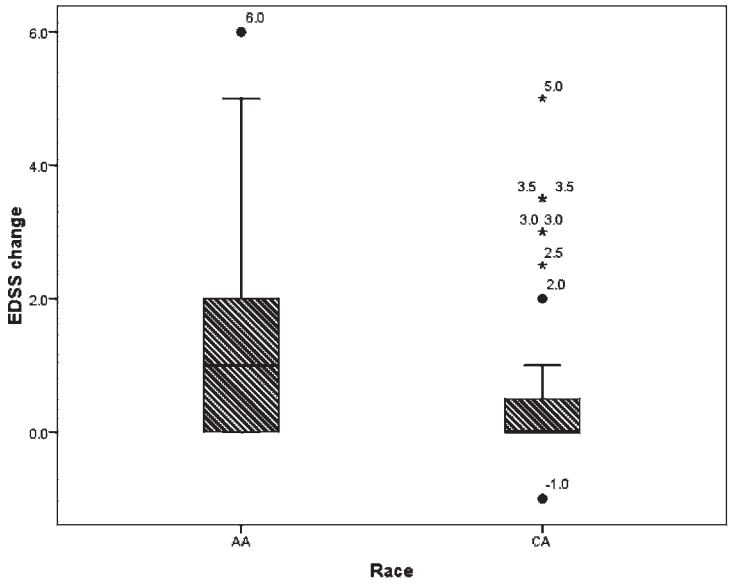

Fig 1. Boxplot in which the box boundaries indicate the 25th and 75th quartiles, the line within each box is the median, the two outer bars indicate the largest and smallest observed values that are not outliers of EDSS differences. $P<.001$ for the Mann-Whitney U (nonparametric) test

We focused our attention on disease duration and EDSS difference. Our results showed that mean disease duration was longer in the CA population (15.1 years in CA patients vs, 7.1 years in AA patients [$P<.001$]). When comparing EDSS difference between the groups, the median EDSS difference was higher in the AA population (median 1.0 in AA patients, 0.0 in CA patients [$P<.001$]). (Figure 1, Table 1).

Given the importance of sex in MS frequency, severity and level of disability, a subgroup analysis was performed and compared the EDSS difference between AA and CA males and females. We found that there was statistically significant difference between median EDSS scores in females (median 1.0 in AA females, 0.0 in CA females [$P=.000$]) (Figure 2). No statistically significant difference was found between the median EDSS in males (median 1.0 in AA males, 0.0 in CA males [$P=.462$]) (Figure 3).

Table 1. Duration of multiple sclerosis, age at diagnosis and expanded disability status scores among African American compared to Caucasians

	AA *n*=66	CA *n*=67	*P*
Sex, *n* (%)			0.36
Female	57 (86.4%)	53 (79.1%)	
Male	9 (13.6%)	14 (20.9%)	
Age in 2010, mean (SD)	41.4 (10.2)	52.0 (9.9)	0
Disease duration, mean (SD)	7.1 (5.5)	15.1 (8.2)	0
Age at diagnosis, mean (SD)	34.3 (9.9)	36.9 (9.9)	0.13
EDSS difference	Median 1.0	Median 0.0	0
	Mean 1.2	Mean 0.5	
	SD 1.4	SD 1.0	
	Min 0.0	Min −1.0	
	Max 6.0	Max 5.0	
	Percentiles	Percentiles	
	25 0.0	25 0.0	
	50 1.0	50 0.0	
	75 2.0	75 0.5	

AA, African American; CA, Caucasian; EDSS, expanded disability status score.

DISCUSSION

The importance of our study is in adding to still limited data suggesting a poorer response of AA patients to DMTs. While there is an increasing amount of data that show more aggressive disease in the AA population, early disability and different phenotype of disease, none of the studies determines the cause of these phenomena.[1,2,4] We found increased disability over a shorter period of disease duration, which could suggest poorer response to DMTs in AA patients. This trend is similar to the nationwide trend that has been suggested previously.[6] Sex sub-analyses showed similar results when the median EDSS difference was compared between females but we were not able to show statistically significant difference in male subgroups. Reduced power among the smaller number of males could be an explanation for this result.

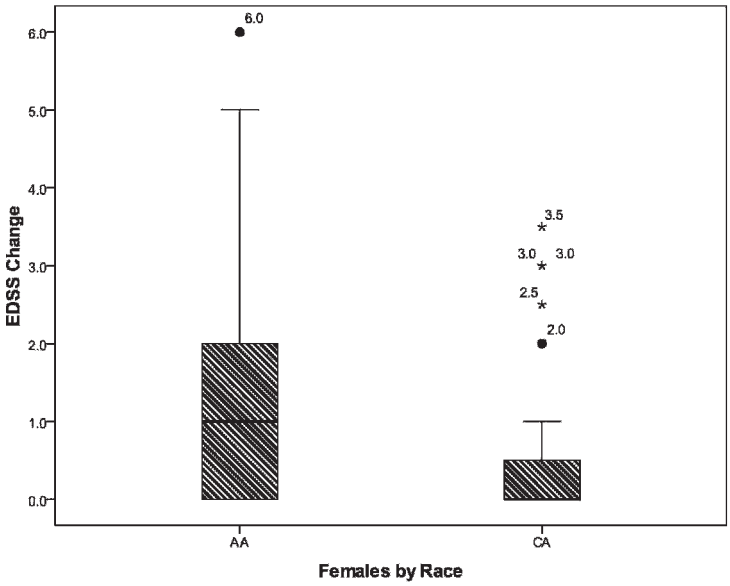

Fig 2. Mann Whitney U test is significant (*P*=.000) for difference in median EDSS difference between CA and AA females

We found increased disability over a shorter period of disease duration, which could suggest poorer response to DMTs in AA patients.

Another unique feature of this study is that it follows only a Southern AA population. This particular population is uncommon in the aspect of relatively little genetic admixture and remains remarkably homogenous. Genetic studies have demonstrated relatedness to the African tribes and low degree of Caucasian genetic influence.[7,8] Like other Southern states, South Carolina experienced an out-migration of African Americans during the first part of the twentieth century, but this tendency reversed between 1960 and 1970. Since then, South Carolina has gained more than 150,000 AAs. This group of immigrants comprised individuals and families with ancestral ties to the state.[9] As such, this particular AA population could represent an opportunity for further research in genetic background of MS in African Americans if adequately powered. Previous studies showed rare incidence of MS among Africans and suggested an inherent genetic resistance or low prevalence of environmental risk factors, but they also described untreated cases with multiple relapses and relatively high severity of the disease.[10,11]

That our results follow a previously suggested trend would further support the theory that differences in genetic background of the AA population are important elements in already described interethnic differences in the clinical course of MS and response to treatment.

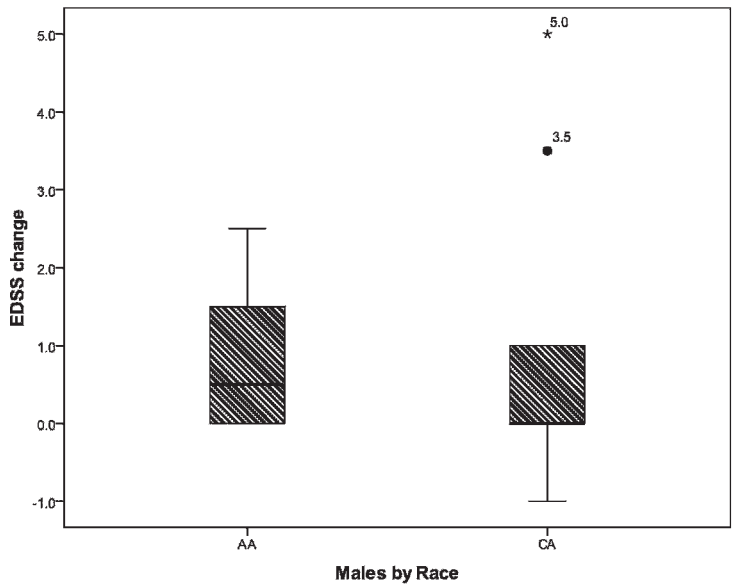

Fig 3. Mann Whitney U test is not significant (*P*=.462) for difference in median EDSS difference between CA and AA males

Studies that show a different response of hepatitis C-infected AA patients to interferon alfa (INF alpha) have been published.[12,13] One of the studies suggested that different host response to affecting agent and distinct disease pathophysiology are responsible for altered INF alpha signaling and treatment response.[12] This could be true for the AA population with MS. It is possible that African ancestry not only provides partial protection against MS, but also, if disease occurs, risk factor for different disease phenotype and different response to treatment. Better understanding of treatment outcomes in populations already known for more aggressive disease and higher level of disability at younger age[14] would help to develop more targeted treatment strategies.

A limitation of this study is its retrospective nature. The EDSS was not a routine part of medical records and frequently had to be derived by the investigator. The majority of the patients followed at MUSC presented for first visit well into their disease course and the EDSS did not represent the score at the time of diagnosis. Therefore, the EDSS difference reported here was calculated for the follow-up period at MUSC (at least a year for all patients).

The chart review and data derivation were not blinded to race, which could cause observation bias. Our study design evaluated disease progression as a function of EDSS difference and did not control for other important confounders such as time to disability milestones. The fact that MUSC is a tertiary care facility could lead to selection bias. Compliance with treatment was based on self-report by the patients and as such prone to report bias. We also did not use imaging as another important mean in assessment of the disease progression.

The majority of the patients were treated with one of the interferons. This decision was clinician-dependent and resulted in not-DMT-agent homogenous population. The sample size of our study group permitted us from performing further subset analyses among treatment agents.

However, despite all the disadvantages of this study, we were able to mimic the previously reported trend in the AA population. Our results further support the need for well-designed prospective studies to better understand the relationship between ethnicity and response to DMTs in MS. These topics could help clinicians to design a more personalized treatment strategy that would improve the outcomes of MS in AA patients.

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AUTHOR CONTRIBUTIONS

Design and concept of study: Klineova, Walker
Acquisition of data: Klineova
Data analysis and interpretation: Nicholas
Manuscript draft: Klineova, Nicholas
Statistical expertise: Nicholas
Administrative: Klineova
Supervision: Walker