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Multiple sclerosis in a multi-ethnic population in Houston, Texas: a retrospective analysis

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Abstract: Multiple Sclerosis (MS) is a progressive neurodegenerative disease that affects more than 2 million people worldwide. Increasing knowledge about MS in different populations has advanced our understanding of disease epidemiology and variation in the natural history of MS among White and minority populations. In addition to differences in incidence, African American (AA) and Hispanic patients have greater disease burden and disability in earlier stages of disease compared to White patients. To further characterize MS in AA and Hispanic populations, we conducted a retrospective chart analysis of 112 patients treated at an MS center in Houston, Texas. Here, we describe differences in clinical presentation, MRI findings, treatment regimens, disability progression, and relapse rate. We found that patients who were evaluated by a neurologist at symptom onset had significantly decreased odds of greater disability [defined as Expanded Disability Status Scale (EDSS) > 4.5] at last presentation compared to patients who were not evaluated by a neurologist (OR: 0.04, 95% CI: 0.16-0.9). We also found that active smokers had significantly increased odds of greater disability both at diagnosis and at last clinical encounter compared to nonsmokers (OR: 2.44, 95% CI: 1.10-7.10, OR= 2.44, 95% CI: 1.35-6.12, p= 0.01, respectively). Assessment of the degree of brain atrophy and progression over time along with enumeration of T1, T2, and gadolinium-enhancing brain lesions did not reveal differences across groups.

Keywords: Multiple Sclerosis; MS; Disparities; Minority populations;

1. Introduction

Multiple Sclerosis (MS) is an autoimmune inflammatory demyelinating condition that affects more than 2 million people worldwide [1,2]. A recent study estimates that in 2017, nearly 1 million adults had MS in the United States [1]. MS leads to an accumulation of disability over time, although disease-modifying therapies (DMT) may lessen long-term disability severity in most patients [3]. MS is considered a heterogeneous disease thought to result from a complex interaction among genetic predisposition, sex, and environment [4]. Increasing evidence suggests that racial disparities are important factors that may explain differences in disease course, prevalence, incidence and outcomes [5–8]. Despite comprising 13.4% and 18.3% of the American population, African-Americans (AA) and Hispanics respectively, remain largely underrepresented and understudied in clinical trials [9–11]. Fortunately, there is an accumulating body of work that characterizes MS in diverse populations, a development that could lead to improvement in our understanding of disease course and epidemiology as well as uncover disparities across various racial/ethnic groups. Better understanding disparities in MS clinical course and outcomes will allow for the development of more effective disease management in patients of diverse backgrounds.

Historically, it had been widely accepted that MS incidence was higher in the White population compared to the AA population [12]. However, population-based cohort studies have challenged this paradigm. A 2013 retrospective cohort study found that AA had a 47% increased risk of MS compared to Whites [13]. Disparities in MS clinical course in minority populations also encompass disability progression, disease burden, symptom presentation, and relapse rates. AA and Hispanics with MS have a higher disease burden and more severe disability in earlier stages of disease than White patients [10, 14–16]. Additionally, AA patients commonly have multi-symptomatic presentations and early motor system involvement [14, 17]. AA also experience inadequate recovery from symptoms and shorter intervals between clinical attacks [8,18]. Furthermore, amongst MS individuals admitted to US nursing homes, AA patients are younger and more disabled than White patients [19]. Studies comparing MRI findings between AA and White patients revealed that the former show both an increased degree of T2 hyperintense lesions and T1 hypointense lesions, which correlate with greater MS-related disability [20].

Clinical data for MS in the Hispanic population is comparatively limited. The few studies on Hispanics suggest a more rapid disability accumulation over time compared to White patients [21–23]. Interestingly, Hispanics were found to have a 50% decreased risk of developing MS compared to Whites [13]. However, several studies concur that Hispanics may have an earlier age of disease onset compared with other patient cohorts [13, 21]. Hispanics and AA with MS are less likely than their White counterparts to visit a neurologist or MS specialist for disease management and have decreased rates of DMT usage due to noncompliance or inappropriate understanding of the treatment plan [24, 25]. DMTs are critical for

effective management and reduction of long-term disability in MS patients. In assessing these data, it is important to consider that the Hispanic population is multiethnic and diverse. Other compounding factors that should be considered include socioeconomic status, place of birth, age of migration to the US, health literacy, systemic biases and systematic racism in healthcare, and access to care [5, 21, 26].

Much of our understanding of MS manifestation and clinical course in minority populations have come from a limited set of studies. Clinical trials on DMTs largely lack data for minorities despite mounting evidence that these groups are at higher risk for a more aggressive disease course [27]. Approximately only 1% of the MS literature focuses on minority populations [10]. The purpose of this study was to address the lack of information by describing the clinical presentation, MRI findings, treatment regimens, disability progression, and relapse patterns in a racially and ethnically diverse population of MS patients in Houston, Texas. Given that the data for this study were collected from a clinic that predominantly serves patients of low socioeconomic status (SES), this study captures ethnic and racial disparities in MS among patients with a similar SES, potentially decreasing the possible effects of confounding factors. This study is critical and timely because it adds to an emerging literature that confirms a disparity in progression of disease in AA and Hispanic MS patients compared to their White counterparts.

2. Patients and Methods

Study Design and setting

Subjects were identified by a retrospective chart review of patients treated at the Smith Clinic Multiple Sclerosis Center. Smith clinic is a unique center that is part of a network that specifically cares for underserved and low socio-economic groups in Harris County, which includes the city of Houston. Additionally, Harris County is the third most populous county in the US. The majority of the patient population seen in the clinic are of Non-Hispanic Black (NH-Black) or Hispanic descent, and Mexicans constitute the majority of the Hispanic population served at the clinic. There is also a small percentage of Non-Hispanic White (NH-White) patients seen in the clinic. For the purposes of this study we are using the terms NH-Black and NH-White to account for the racial diversity of Hispanics seen in our clinic. Patients are attended to irrespective of insurance status or ability to pay.

Cohort Identification and selection

Information from all patients who visited Smith clinic from March 2019 to March 2020 were identified through chart review and included in this retrospective study. All patients with a diagnosis of Relapsing Remitting MS (RRMS), Secondary Progressive MS (SPMS), or Primary Progressive MS (PPMS) were included.

Outcome measurements

The following pre-selected information was abstracted for each patient: year and age of first symptoms, age at diagnosis, the amount of time that elapsed between onset of symptoms and diagnosis, disease subtype, estimated Expanded Disability Status Scale (EDSS) at diagnosis and last encounter, Disease Modifying Therapy (DMT) history (adverse reactions, relapses, and changes in immunomodulatory therapy), radiological findings, number of clinical relapses, smoking status, and autoimmune comorbidities. Escalation therapies included Glatiramer Acetate, Interferons, Teriflunomide, Dimethyl Fumarate and Fingolimod. High efficacy therapies included Rituximab, Ocrelizumab, Alemtuzumab and Natalizumab. Symptoms at disease onset were recorded and included motor, sensory, cerebellar, brainstem, bowel, and bladder function among others.

Data collection and management

Two neurologists extracted patient data from medical records and the study protocol was approved by our Institutional Review Board. Information from the most recent clinical encounter and from the clinical encounter at diagnosis were included. The EDSS at presentation was estimated based on the first documented neurologic examination by a neurologist and was not indicative of the maximal neurologic deficit during the demyelinating episode that led to the diagnosis. A severe disability was defined as an estimated EDSS score > 4.5 . MRI interpretations were collected from radiology reports. Lesion quantification and atrophy scoring were extracted directly from radiology reports and raw images were not independently interpreted by the neurologists gathering the data. A relapse was defined as a new, documented, neurological complaint lasting more than 24 hours with objective findings in the documented neurological exam, or a follow-up MRI showing new enhancing lesions.

Statistical Analysis

The statistical analyses were performed using R (version 3.6.1) and RStudio (Version 1.2.5001). Based on the race and ethnicity information of the patients, we created a composite variable called 'race/ethnicity' and categorized the responses as Non-Hispanic (NH) White, NH-Black, Hispanic and 'others'. We conducted descriptive statistics on patient socio-demographic and disease characteristics stratified by race/ethnicity. We conducted Fisher's exact tests (for categorical variables) and ANOVA (for continuous variables). We examined the usage and impact of DMTs across racial/ethnic groups. We also examined various markers of disease progression including lesions and atrophy in the brain as well as the thoracic and cervical spine stratified by race/ethnicity using Fisher's exact test. Applying adjusted Exact logistic regression models, we evaluated the association between various patient characteristics and a high EDSS score (EDSS > 4.5). Models were

adjusted for different covariates based on the literature and context, along with experts' recommendations. All analyses were based on two-tailed probabilities with a type 1 error rate set at 5%.

3. Results

Data from a total of 114 patients were analyzed in this study. Two patients were excluded due to a substantial amount of missing information. Of the included 112 patients, most were diagnosed with Relapsing Remitting MS (RRMS). About 73% of NH-White, 92% of NH-Black, and 95% of Hispanic patients had RRMS, whereas only 18% of NH-White, 5% of NH-Black, and 2.5% of Hispanic patients were diagnosed with Primary Progressive MS (PPMS) (Table 1). One Hispanic patient had a diagnosis of SPMS. There were no significant differences among the groups with regard to MS type at diagnosis ($p = 0.1859$), or smoking status ($p = 0.3079$). All groups had a similar female to male ratio, with a greater proportion of female MS patients (Table 1, $p = 0.3675$). Average age at diagnosis ($p = 0.9918$) and mean time to diagnosis ($p = 0.9934$) were also similar across all groups (Table 1).

Notably, only 28% of the NH-Black population had received an evaluation by a neurologist at symptom onset, whereas 53% of Hispanic and 45% of NH-White patients had, although this was not statistically significant (Table 1, $p = 0.1778$). In this cohort, there were no statistically significant differences in receipt of a medical evaluation at symptom onset; 63-70% of patients from all groups were able to access medical evaluation. Additionally, NH-White, NH-Black and Hispanic patients exhibited no differences in symptoms at diagnosis or mean EDSS score at diagnosis and last encounter (Table 2). There was a significant difference in the percentage of patients with severe disability (EDSS score > 4.5) at diagnosis and at last encounter; 14.3% of NH-White MS patients had severe disability at diagnosis compared to 50% of NH-Black and 31.6% of Hispanic patients (Table 2, $p < 0.001$). This was also true at last encounter with 32.5% of NH-White, 45.5% of NH-Black and 41% of Hispanic MS patients with severe disability at their most recent clinical visit (Table 2, $p < 0.001$).

Assessment of degree of brain atrophy and progression over time revealed that NH-White, NH-Black and Hispanic patients in this cohort had a similar degree of brain atrophy at diagnosis and over time (Figure 1). Enumeration of T1, T2, and gadolinium-enhancing brain lesions at diagnosis also showed no significant differences between the groups (data not shown). Spinal atrophy and quantity of T2 and gadolinium-enhancing lesions in the spine at diagnosis and at last presentation were also similar between groups (Figure 2).

Table 1: Subject characteristics.

| Characteristics | NH-White (N=11) | NH-Black (N=61) | Hispanic (N=40) | P value |
|---|--------------------|--------------------|--------------------|------------|
| Multiple Sclerosis (MS) type at diagnosis | | | | p = 0.1859 |
| Relapsing remitting MS | 82% | 95% | 95% | |
| Primary progressive MS | 18% | 5% | 2.5% | |
| Secondary progressive MS | 0% | 0% | 2.5% | |
| Mean Age at diagnosis (years) | 39.9 (11.3) | 36.7 (11.4) | 32.4 (11.5) | P = 0.9918 |
| Female/Male ratio | 1.70/1 | 2.33/1 | 1.22/1 | p = 0.3765 |
| Active smokers | 55% | 44% | 30% | p = 0.3079 |
| Mean time from symptom onset to diagnosis (months) | 30.8 | 32.9 | 13.7 | p = 0.9934 |
| Medical Evaluation at symptom onset | 64% | 63% | 70% | p = 0.8597 |
| Neurological Evaluation at symptom onset | 45% | 28% | 53% | p = 0.1778 |

EDSS score at diagnosis and last EDSS score were compared within each group. p = 0.4253 (NH-Black), p = 0.1757 (Hispanic), p = 0.0324 (NH-White), (paired sample t-test).

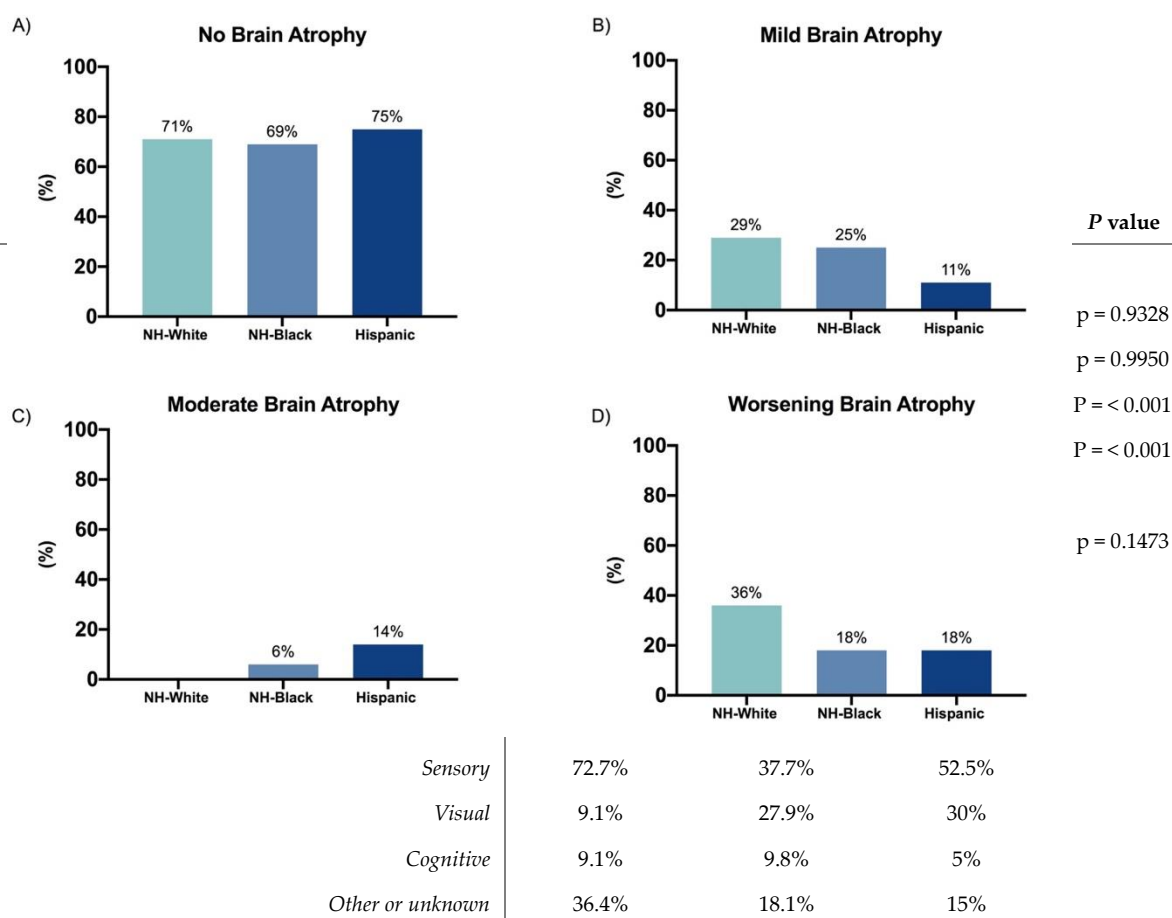


Figure 1: Degree of brain atrophy at diagnosis and worsening of brain atrophy from diagnosis to most recent MRI scan. Presented as the total percentage of each group, is the proportion of patients who had none (A), mild (B), or moderate (C) brain atrophy at the time of diagnosis, as well as the proportion of patients who had increased brain atrophy in their most recent MRI scan compared to diagnosis (D). Only patients who had MRI scans on file were included in this analysis. $p = 0.5155$ for comparison between degree of brain atrophy (none, mild, moderate) (Fisher's exact). $p = 0.3387$ for comparison of total percentage of patients who had worsening brain atrophy on most recent MRI compared to diagnosis (Fisher's exact).

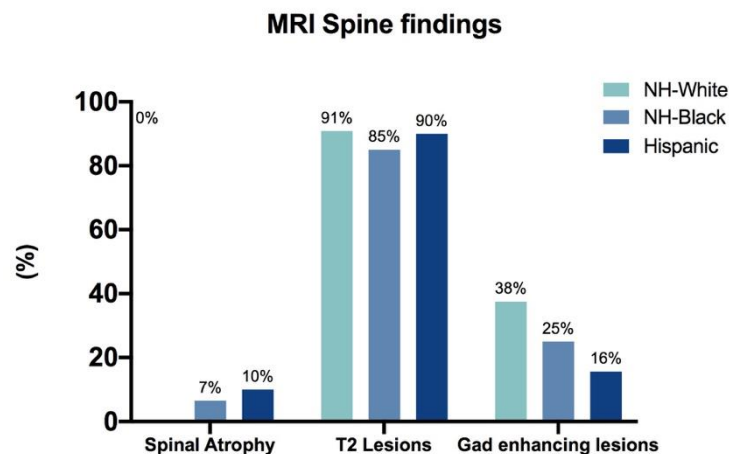


Figure 2: The total percentage of patients in each group who had spinal atrophy, T2, or gadolinium-enhancing lesions in the spine as determined by MRI findings at diagnosis. Only patients who had MRI scans on file were included in this analysis. $p = 0.6974$, $p = 0.5128$, $p = 0.2957$ for comparison of total percentage of patients in each group that had spinal atrophy, spinal T2 lesions, and spinal gadolinium-enhancing lesions respectively (Fisher's exact).

Table 3: Association between various patient characteristics and high EDSS score at last presentation (>4.5)

| High EDSS score at last presentation | | |
|--|------------------|---------|
| | OR | p-value |
| Usage of escalation therapies^a | | |
| No | reference | |
| Yes | 1.60 (0.45-6.14) | 0.48 |
| Usage of high efficacy therapies^b | | |
| No | reference | |
| Yes | 2.64(0.87-8.33) | 0.09 |
| Smoker^c | | |
| No | reference | |
| Yes | 2.44(1.36-6.12) | 0.01 |
| Medical evaluation by Neurologist^c | | |
| No | reference | |
| Yes | 0.40(0.16-0.90) | 0.04 |
| Adherence to DMT^c | | |
| Yes | reference | |

| | | |
|---|-----------------|------|
| No | 0.73(0.31-1.62) | 0.43 |
| Time to diagnosis^c | | |
| <=12 months | reference | |
| >12 months | 1.73(0.75-4.01) | 0.2 |
| a - adjusted for adherence, smoking, race and age and EDSS at diagnosis | | |
| b- adjusted for prior exposure to escalation therapies, adherence, smoking, race, age and EDSS at diagnosis | | |
| c-adjusted for age and race | | |

Patient usage of escalation or high efficacy therapies did not significantly impact the patient's likelihood of having an EDSS score > 4.5 at last clinical encounter after adjustment for adherence, smoking, race, age, prior exposure to escalation therapies, and EDSS at diagnosis (Table 3). Active smokers were 2.44 times as likely to have an EDSS score > 4.5 at their last clinical encounter compared to non-smokers after adjustment for age and race (OR: 2.44, 95% CI: 1.36-6.12, $p = 0.01$) (Table 3). Interestingly, after adjustment for race and age, patients who were evaluated by a neurologist at diagnosis had significantly lower adjusted odds of an EDSS score > 4.5 at last presentation compared to patients who were not evaluated by a neurologist (OR: 0.40, 95% CI: 0.16-0.90, $p = 0.04$) (Table 3).

Table 4: Association between various patient characteristics and high EDSS score at diagnosis (>4.5)

| High EDSS score at diagnosis | | |
|--------------------------------------|-----------------|---------|
| | OR | p-value |
| Smoker^c | | |
| No | reference | |
| Yes | 2.79(1.10-7.10) | 0.01 |
| Time to diagnosis^c | | |
| <=12 months | reference | |
| >12 months | 1.15(0.46-2.83) | 0.77 |
| c-adjusted for age and race | | |

Active smokers were 2.79 times as likely to have an EDSS score > 4.5 at diagnosis compared to non-smokers after adjustment for age and race (OR: 2.79, 95% CI: 1.10-7.10, $p = 0.01$) (Table 4). There was no significant association between time to diagnosis and having a high EDSS score at diagnosis (Table 4). There were no significant differences in total relapse occurrence for patients on escalation therapy vs. high efficacy therapy for each racial/ethnic group (Data not shown). Of 24 NH-white patients, 19 had ever used escalation therapy and 5 had used high efficacy therapy. Of 93 NH-Black patients, 74 had used escalation therapy and 19 had used

high efficacy therapy. For the Hispanic patients group, of 63 patients, 55 had ever used escalation therapy while 18 had documented use of high efficacy therapy. We found no differences between the groups with respect to usage of escalation vs. high efficacy therapies.

4. Discussion

This retrospective cohort study demonstrates racial/ethnic differences in multiple sclerosis presentation and disease course. Interestingly, after adjustment for race and age, patients who were evaluated by a neurologist at diagnosis had 60% lower odds (OR= 0.40, 95% CI: 0.16-0.90) of an EDSS score > 4.5 at last presentation compared to patients who were evaluated by a non-neurology specialist. This suggests a logical protective effect of treatment by a neurologist at symptom onset and highlights the importance of access to treatment for all patients. Indeed, a national descriptive study found that people with MS who saw a neurologist were more likely to receive appropriate DMT treatment and see rehabilitation and urologist specialists compared to people who saw other providers [28]. A 2017 study on racial disparities in neurologic health care access revealed that Black patients were 30% less likely to see an outpatient neurologist and were more likely to be cared for in the emergency department compared to their White counterparts [24]. Similarly, Hispanic patients were 40% less likely to see an outpatient neurologist compared to NH-Whites [24].

We found that actively smoking patients were 2.44 times as likely (95% CI:1.36-6.12) to have severe disability at diagnosis, and at the last clinic follow up. A recent systematic review and meta-analysis found evidence supporting the causal involvement of smoking in the development and progression of MS [29]. Altogether, these data suggest that smoking prevention and cessation education programs as well as an early intervention by a neurologist should be implemented in order to achieve optimal MS care in diverse patient populations.

Consistent with published reports, NH-Black patients had a higher risk for early severe disability (defined in our study as an estimated EDSS > 4.5) when compared to NH-White and Hispanic patients [30,31]. In our present study, treatment modality did not impact the risk of having an estimated EDSS > 4.5 score at the last visit. Nonetheless, we observed a trend towards a higher relapse rate in escalation therapies vs. high efficacy therapies, especially in NH-Blacks. Other studies have found that NH-Black patients treated with interferons experienced more relapses and new MS lesions on T2-weighted brain magnetic imaging than NH-Whites [32]. Nonetheless, further studies on the interaction between ethnicity and DMT response for MS are necessary.

Several studies have shown that African Americans have significantly higher CNS lesion burden, more frequent relapses, worse ambulatory disability, worse post-relapse recoveries, and higher overall disability at diagnosis [5, 10, 20, 30]. Although

there appeared to be an increase in the degree of atrophy and MRI involvement in NH-Black compared to other groups, the trend observed in our study was not significant.

Limitations of this study include its retrospective nature, the variable periods of follow-up and the selection of therapy by the treating physician (nonrandomized). The study was also constrained by a small sample size which could have induced a type 2 error leading to the inability to reject the null hypothesis in some of our comparisons.

Taken together, our study is important because it adds to an emerging literature suggesting a more aggressive disease in minority populations with MS. The disparities in MS progression, onset, and disease course warrants further study. Of 60,000 published articles on MS, only 113 focused on NH-Black and only 23 focused on Hispanic American patients with MS as of 2014 [10]. This demonstrates a need for studies that are intentionally inclusive of these populations. Since 2014, there has been a modest but steady increase in studies focused on these populations. There is a clear disparity in MS treatment access for patients from different racial and ethnic backgrounds. Drivers of disparity are often comprised of complex interactions among factors such as socioeconomic status, access to healthcare and wellness resources (clinics, hospitals, grocery stores, fitness centers), systemic racism and biases in healthcare, and limited health literacy. This systemic web of disparity can be challenging to disentangle, but understanding it is necessary for improving the care of minority patients with MS.

Future prospective randomized controlled trials in different racial/ethnic groups with MS are essential to better understand the disease progression, management and treatment outcomes for diverse patient populations.

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