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Race and Ethnicity on MS presentation and Disease Course: ACTRIMS Forum 2019

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Abstract

Multiple Sclerosis (MS) has a strong racial and ethnic component and disproportionately affects whites of European background. Recent incidence reports suggest an increasing rate of MS among African Americans compared with whites. Despite this recent increase in MS in African Americans, Hispanics and Asians are significantly less likely to develop MS than whites of European ancestry. MS-specific mortality trends demonstrate distinctive disparities by race/ethnicity and age, suggesting that there is an unequal burden of disease. Inequalities in health along with differences in clinical characteristics that may be genetic, environmental, and social in origin may be contributing to disease variability and be suggestive of endophenotypes. The overarching goal of this review was to summarize the current understanding on the variability of disease that we observe in selected racial and ethnic populations: Hispanics and African Americans. Future challenges will be to unravel the genetic, environmental and social determinants of the observed racial/ethnic disparities.

Keywords

Multiple sclerosis; race; ethnicity; health disparity; genetic ancestry

Introduction:

Multiple Sclerosis (MS) is a genetically complex autoimmune disease with an incidence and prevalence that is reported to differ with race and ethnicity.(1) World distribution supports that northern latitudes have the highest prevalence of MS(2) and that its considerably lower in Asian and Hispanic populations. However, the incidence of MS for African Americans is increasing(3, 4) which could suggest both environmental and genetic changes. On the other hand, Hispanics are increasingly reported among pediatric MS cohorts(5) with an overall younger age of onset noted among Hispanic adult cohorts.(6, 7) The variability in clinical presentation and disease severity reported for both groups could suggest an MS endophenotype that could be used to identify high-risk individuals. In this review, we summarize current observations and trends that highlight ramifications that stem from the

complexity of race and ethnicity as a composite variable in disease presentation, severity and progression. Focusing on African Americans and Hispanics we hope to present a framework to further explore the concept of race and ethnicity in MS and its related health disparities.

Definitions behind Race and Ethnicity

Race and ethnicity are widely used interchangeably in population research. However, more often it is used as a simple demographic variable where the methods to arrive at categorization are seldom discussed. The use of self-identification combined with physical characteristics and medical records could provide a better framework when examining race and ethnicity in disease. Race presumes a person's physical appearance (i.e. skin color) and biological differences that may concern phenotype or genotype in disease. Ethnicity tries to infer societal differences related to cultural heritage, language and other social and geopolitical factors.(8) While informative and helpful in clustering individuals with common features and background, they do not reveal the extent of genetic admixture in an individual's ancestry. This is particularly important to consider in a disease such as MS where both genetics and race play a role. The genetic admixture of both African Americans and Hispanics across the United States (US) differ in the proportion of European and African genetic background as well as Native American proportions between Hispanic ethnicities.(9) These admixture differences are the result of geopolitical changes and migrations that occurred between continentally divided ancestral populations within the past 200–500 years leading to genetic variant frequency differences among these various groups. (9) For example the use of a single Hispanic ethnic category is insufficient to distinguish genetic variability between Mexican and Puerto Rican populations, which could be important when examining why a certain disease that has a genetic basis is more common among individuals with Puerto Rican ancestry versus those individuals of Mexican ancestry. On average, our own work in Hispanics with MS further highlights the genetic ancestral differences between Hispanic groups; Mexican-Americans have a higher proportion of Native American ancestry (~38%) but lower African ancestry (average 7%) than Puerto Ricans who have on average 15% or higher African ancestry (Figure 1).(10, 11)

Summary: Race and ethnicity, combined, is a multidimensional construct that reflects exposure to external health risks posed by environmental, genetic, social, and behavioral factors. Examining the ancestral heterogeneity in Hispanics and African Americans, could help detect genetic variation which can be used as a tool to sort biological from non-biological explanations of MS.(9)

Methodologies in Determining Race/Ethnicity

Changing demographics in MS are suggested by large multiethnic datasets in the US. Electronic medical records (EMR) have been successfully used to improve patient care and obtain important information on demographic and clinical characteristics. Not neglecting their importance to our understanding of MS, the reliance on race and ethnic categorization using EMR and death certificates can sometimes be problematic and lead to an underestimation of certain ethnic minority groups.(12, 13) Lower sensitivity and positive predictive values have been reported when comparing ethnicity of Hispanics (0.55 and 0.81, respectively) and Native Americans (0.47 and 0.50; respectively) from hospital admissions

records compared to self-reported study interviews.(14) Misclassification of race and ethnicity has also been reported when comparing EMR to birth certificates with the lowest percent correlations being reported for Asian, Native American, and those that report as multiple ethnic/racial background (~18–74%).(13) A separate study reported that the classification of race and ethnicity on death certificates between 1999–2011 were not significantly problematic for Hispanics.(15) However, misclassification remained high at 40% for Native American related ancestry. Thus, Asian, Native American, and Hispanic groups are more likely to be underestimated.

MS Prevalence/Incidence and Race/Ethnicity

In the last several years, changes in the demographics of MS have been reported around the world.(3, 16, 17) In the US, both African Americans and Hispanics are being increasingly diagnosed and recent studies reflect changes that contradict the once held belief that African Americans were a low MS risk population. A retrospective cohort study using electronic medical records from the Kaiser Permanente plan in Southern California reported African Americans to have a 47% increased risk of MS, while Hispanic Americans had a 50% lower risk and Asian Americans had an 80% lower risk of MS compared with white Americans (2.9 per 100,000 for Hispanics vs. 6.9 for whites).(3) Wallin and colleagues, using data from the US military Veteran population, also reported similar observations indicating higher rates of MS in African Americans.(4) Lower risk of MS in both studies was consistently reported for Hispanics and Asians. Interestingly, a Canadian study reported the incidence of MS to be increasing among females of Asian background living in British Columbia where the incidence doubled during the period of 1986–2010 while the non-Asian white population remained unchanged.(17) The explanation for these changing demographics are unknown but certainly could reflect environmental and social factors but less so genetic susceptibility as changes would be too rapid to be explained by genetic alterations.

Mortality and Race/Ethnicity

MS-specific mortality trends also demonstrate distinctive disparities by race/ethnicity and age, suggesting that there is an unequal burden of disease.(18) While limited, mortality rates in the US have been reported to be the highest in whites followed by blacks with Asians and Hispanics having the lowest rates.(19) Using the compressed mortality data file for 1999–2015 in the wide-ranging online data for the Epidemiological Research System developed by the Center for Disease Control and Prevention in the US, we calculated the age-adjusted and age-specific MS mortality rate by sex and five distinct ethnic groups: Hispanic, non-Hispanic (NH) black, NH white, NH Asian Pacific islander and NH American Indian and Alaska Native.(18) While an increasing trend in age-adjusted MS mortality was observed during 1999–2015 among NH whites and NH blacks, age-specific MS mortality patterns highlighted NH black males as the greatest group at risk particularly before age 45. This US based study suggests that the burden of disease weighs differently by race and ethnicity, which has also been previously suggested by studies using the North American Research Committee for MS registry, which includes both US and Canadian enrollees.(20) Disparities in mortality rates between racial and ethnic groups should raise questions about particular characteristics in these groups, including the co-existence of comorbidities and/or alternate diagnoses that can mimic MS, have a higher prevalence, and are associated with higher

morbidity and mortality (e.g. neuromyelitis optica (NMO) spectrum disorders(21, 22)) in African and Hispanic backgrounds.

Race and ethnic clinical variability in MS:

Multiple observational studies suggest that African Americans and Hispanics have unique clinical characteristics that could be the result of genetic and environmental factors.(23) These reports reflect less than 1% of the published literature in MS(24) but nevertheless suggest that variations in MS clinical, Magnetic Resonance Imaging (MRI), disease severity and progression are the result of complex interactions between genetic predispositions and environmental factors that could be reflective of endophenotypes.(25)

Race and Ethnicity and Age of Onset of MS:

African Americans have been reported to develop MS both at an earlier(26) and at a later(27) age compared with whites. These discrepancies in age of onset have not been rectified, but interestingly the studies appear to differ by region of ascertainment such that the earlier age observation came from the east coast and the older age reflected a west coast African-American population. Hispanics are also reported to present with MS at a younger age compared with whites(3, 6, 7, 26) and African Americans.(3, 26) Self-identified US Hispanics are found to develop MS 3–5 years younger compared to non-Hispanic whites and this younger age of onset is further seen for those Hispanics born in the US compared to those that are foreign born. Age of onset was also significantly younger ($p > 0.001$) for those who were US born compared to immigrant Hispanics from Latin America to the US at adolescent age or older with 74% developing MS in the US on average 15 years later from age of immigration.(7, 28) This observation continues to be consistent across other regions of the US(6) and other countries where migration has occurred between lower to higher latitudes.(29) These data favor the influence of environmental risk factors to be age dependent and suggests that birth and residence at higher geographic latitudes are also factors important in the development of MS in Hispanics.

Environmental risk factors for MS associated with Race and Ethnicity

Recent multiethnic investigations into the cause of MS have reported that known environmental risk factors in white non-Hispanic populations may not be as relevant in African Americans and Hispanics.(30–32) Epstein-Barr virus has been consistently associated with the risk of MS and recent studies also support that being Epstein-Barr nuclear antigen-1 seropositive is associated with an increase odds of getting MS across diverse ethnic backgrounds: African Americans, Hispanics and whites. However, CMV seropositivity was only found to be associated with a lower risk of MS in Hispanics ($p = 0.004$) and having been born in a low income country appeared to contribute to being seropositive. These differential observations behind CMV could suggest that timing of exposure is due to social and behavioral differences not only between cases and controls but also by race and ethnicity. Evaluating vitamin D as a risk factor in the same multiethnic cohort and the development of MS however further confirmed that having higher serum levels of 25OHD is associated with a lower risk of MS in whites, but no association was found in Hispanics or blacks. Nevertheless, a higher lifetime ultraviolet radiation exposure

appeared to be statistically significant in lowering the risk of MS in blacks and whites but not in Hispanics. A follow-up study involving the same population evaluated whether these negative results in blacks and Hispanics could be best explained by differential polymorphisms in the vitamin D-binding protein gene. Interestingly, dominant polymorphisms in the vitamin D-binding protein gene were not helpful in explaining the lack of association between 25OHD and MS in blacks and Hispanics. These studies challenge the notion that MS risk factors are equal across populations but underscore the greater effect of race and ethnicity on MS.

Genetic Risk Factors for MS associated with Race and Ethnicity

Genetic factors have also been reported to influence age of onset using minority cohorts. A study of African Americans with MS reported that African Ancestry at the human leukocyte antigen (HLA)(33) influences clinical outcomes in this population. African Americans with MS who were carriers of the (HLA)DRB1*15 allele were twice more likely to have an earlier age of onset and had a 2.1-year younger mean age at disease onset compared to those not carrying DRB1*15 alleles. (33) Additionally, genetic variants from non-HLA risk genes reported in white MS cohorts have been tested in an African American cohort noting a trend of an effect on earlier age of onset in those individuals carrying the risk variant within the *RGS1* gene locus.(34) Suggestions of potential genetic factors related to Hispanic ancestry influencing age of onset are also evident by our recently published study in self-identified Hispanics.(11) As part of our research efforts within the Alliance for Research in Hispanic MS (ARHMS) consortium, we evaluated the association of global genetic ancestry with age at first symptom in a large (n=1033) well-characterized multi-center cohort. Using multivariate linear regression we observed a significant association between genetic ancestry and age of first symptom ($P=6.37 \times 10^{-04}$; joint test of Native American and African ancestry). Both an increase in African (beta=-10.07, $P=1.39 \times 10^{-03}$) and Native American (beta=-5.58, $P=3.49 \times 10^{-02}$) ancestry contributed to a younger age at first symptom.(11)

Summary: Geographical location before onset of multiple sclerosis remains a risk factor in MS and studies of both African and Native American genetic ancestry demonstrate an increased risk for younger age of onset. While our data lend support to this hypothesis, we recognize the need for more complete environmental studies that integrate genetic ancestry and migration details. These observations underscore that an earlier age of onset is an expected feature of minority MS and may confer prognostic value.

Race and Ethnicity and Disease Severity and Progression:

There are racial and ethnic effects that suggest both African American and Hispanics when compared to whites to be high-risk populations for early disability and worse prognosis.(1) Using the Patient-Derived Multiple Sclerosis Severity Score (P-MSSS) significantly higher disability scores have been reported for both Hispanics (3.9 ± 2.6) and African Americans (4.5 ± 3.0) compared to whites (3.4 ± 2.6 ; $p < 0.0001$; adjusted for age).(26) Additional measures supporting greater disability in African Americans stem from optical coherence tomography (OCT) studies and MRI where recently greater accelerated retinal damage over time(35, 36) and brain tissue loss, including regional brain atrophy(35) changes, have been reported compared to whites. While imaging measures concerning Hispanics are nearly

scarce, disability measures have been reported to differ by age of immigration to the US and place of birth. Foreign born and older age of immigration to the US were found to be independently associated with increased ambulatory disability (adjusted OR 2.3, 95% CI 1.07–4.82; $p=0.03$).⁽²⁸⁾

Summary: The mechanisms accounting for these differences in disability measures between whites and minority populations with MS here in the US are still poorly understood. The potential for confounders such as environmental and social factors makes it hard to generalize that MS is more aggressive in minorities. Nevertheless, studies in immigrants to the US that develop MS years later and coming from lower prevalence regions offer a unique opportunity to explore the effects of environmental and diet changes. Obtaining data related to changes that accompany migration may facilitate an opportunity to evaluate known risk factors as well as identify potential new triggers or modifiers. However, barriers to obtaining these types of data will include the geopolitical environment pertinent to new immigrants to the US.

Disparities in Health Outcomes

African Americans and Hispanics make-up nearly 30% of the US population and are geographically unequally distributed throughout the country (web 1). Being a minority in the US has strong links to health disparities due to social disadvantages. Disadvantages are characterized by such factors as living in poverty, being poorly educated, and other socioeconomic factors. Health disparities are defined as avoidable differences in health status, mortality and burden of disease that disproportionately affects some groups despite having similar characteristic such as gender.^(37, 38) While health inequity and health disparity are intertwined, health inequities are health disparities in the access to or availability of health-related facilities and services.⁽³⁸⁾ Thus, social, economic, and environmental circumstances in which these minority groups are born to and are living in could account for some of the clinical variations in disease severity. There is evidence supporting health literacy problems when it comes to MS related disease modifying treatments and their realistic expectations,⁽³⁹⁾ poor access to specialty care, and illness perceptions affecting self-care.^(40, 41) Analysis of individuals with MS using the Independence Care System, a Medicaid long-term managed care plan in New York, found several deficiencies in the care of low-income minorities with MS where 30% had never seen an MS specialist and another 30% were not taking disease modifying treatments due to poor compliance and understanding of the drug.⁽³⁹⁾ Similar access problems were recently reported using a nationally representative dataset from the 2006–2013 Medical Expenditure Panel Survey where both blacks and Hispanics with MS were less likely to see a neurologist compared to whites (30% and 40% less, respectively).⁽⁴⁰⁾

Summary: Proper care access, health literacy, and illness perceptions affect adults in all racial and ethnic groups, with a greater proportion reported in US minorities. Future studies that incorporate factors related to healthcare system, provider-patient relationships, and the patient's and community needs, beliefs and expectations,⁽⁴²⁾ would support a more inclusive way of studying outcomes in MS.

Future Directions:

Understanding the effect of race/ethnicity is crucial in understanding MS disparities. Whether there are racial and ethnic group characteristics that would relate to an endophenotype is still unclear. Studying the impact of genetic and environmental variation, and ancestry and its relationship to health disparities on MS across populations will help ensure that precision medicine efforts will be impactful to all groups. Minorities with MS face greater barriers related to access and education in MS care. Additionally, clinical trials have <10% clinical trial participation from minorities(43) which should call into question efficacy profiles of disease modifying treatments. This lack of representation is not well understood but may reflect minorities having less access to specialists who are more likely to be at specialty care centers that recruit subjects for clinical trials. The fear of exploitation, due to a not too distant past history of unethical medical testing in the US (i.e. Tuskegee experiments and others) and lack of time or financial resources to participate and other competing barriers add another layer of complexity when examining race and ethnicity in MS.(24) Collaborative research networks that strive to develop trust and teamwork with the community, such as the Alliance for Research in Hispanics MS(44) (Web 2) and the Minority Research Engagement Partnership, could help further these research efforts.

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	UM	PR	USC
European	82%	72%	55%
African	9%	15%	7%
Native American	9%	14%	38%

Figure 1:

The distribution of global ancestry proportions for self-identified Hispanic MS cases by ascertainment site within Alliance for Research in Hispanic MS (ARHMS). Predominantly Caribbean Hispanic patients ascertained at both the University of Miami (UM; n=150) and within Puerto Rico (PR; n=150) versus largely Mexican-American ascertainment at the University of Southern California (USC; n=150).