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DEMYELINATING DISORDERS (J. BERNARD & M. CAMERON, SECTION EDITORS)

Clinical Characteristics of Multiple Sclerosis in African-Americans

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Abstract

Purpose of Review Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that affects nearly 1 million people in the USA and has the potential to profoundly affect physical ability and income potential at a young age. Since a landmark paper was published in 2014, few studies have looked at differences in MS disease characteristics between African-American and Caucasian patients.

Recent Findings African-American patients often have a more severe MS disease course, as well as biomarker data which can portend a worse prognosis. While the sample sizes are usually quite small, subgroup analyses of African-American patients have been performed to evaluate efficacy of disease-modifying treatments as compared with the entire study population, made up of primarily Caucasians.

Summary In an era where we strive for personalized medicine, understanding racial differences in MS may help us better treat African-American patients in the future.

Keywords Multiple sclerosis · African-Americans · Progression · Disease severity

Introduction

Multiple sclerosis is an autoimmune disease of the central nervous system that affects nearly 1 million people in the USA [1] and has the potential to profoundly affect physical ability and income potential at a young age. The cause is unknown, but it is thought to be a complex interaction between genetic risk and exposure to various environmental factors. MS has classically been described as a disease of young Caucasian women, which is why many minority patients (including African-Americans) present to clinic in disbelief of the diagnosis. However, according to at least one study, it appears that the incidence of MS is higher in African-Americans than any other ethnic/racial group, with black women having a higher risk of developing MS than white women (men have similar risks) [2]. In a 2014 PubMed literature review, Khan et al. found only 113 articles published about MS in African-Americans, out of nearly 60,000 articles in total [3]. In the last 5 years, there have been fewer than 30 articles published with the same characteristics. The focus of these articles includes response to disease-modifying therapy, and measurement of risk or disease severity in different racial groups. Studying the racial differences in patients with MS is important because there are differences in disease localization in the CNS as well as severity of disease between racial groups. Perhaps a better understanding of these disparities can lead to the discovery of more personalized treatments. This article will provide a brief overview of racial disparities in MS research that, to date, have gone underexplored in the literature, and will explore some of the possible consequences of those disparities.

Disparities in Socioeconomic Status and Access to Healthcare

The failure of MS research to include African-Americans has several significant potential consequences for patient care. African-Americans (as well as other minority groups) are underrepresented in clinical trials for disease-modifying treatments of MS, and therefore, the results of these studies may only be generalizable to Caucasians. Without studying diverse groups of patients, common disease-modifying therapies for

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MS may not be as effective in minority patients. Further, other factors such as health literacy, access to healthcare, and social beliefs may also (unfairly) determine who receives effective treatment for MS. Racial disparities in health insurance coverage exist where African-Americans have longer periods of time where they are uninsured or underinsured than Caucasian Americans [4]. A real-life example of where a lapse of insurance coverage costs someone their ability to walk happened to one of my patients. She was walking with a cane while on a disease-modifying treatment for MS, but then lost her insurance and therefore her access to her immunomodulatory medication. During this lapse, she developed a severe rubral tremor which left her unable to ambulate at all, because the tremor prevents her from steering a four-wheeled walker. These kinds of lapses in healthcare coverage are incredibly detrimental to any patient with a chronic disease, especially in the case of multiple sclerosis, in which a new relapse can cause severe permanent disability (Fig. 1).

One theory of why there are differences in disease severity between races is attributed to differences in socioeconomic status. Upon review of the existing literature, racial disparities in socioeconomic status do not appear to fully explain the disparity in disease severity among African-American patients. For example, African-American MS patients are at a higher risk for spinal cord disease, increased number and severity of relapses, disability following a relapse, faster transition from relapsing to progressive MS, and more severe impairment in ambulation [3]. Theoretically, it is possible that these patients are of lower socioeconomic status and thus uninsured or underinsured, which prolongs their time to effective treatment and thus worsening their symptoms. It is widely accepted that early treatment of MS improves long-term

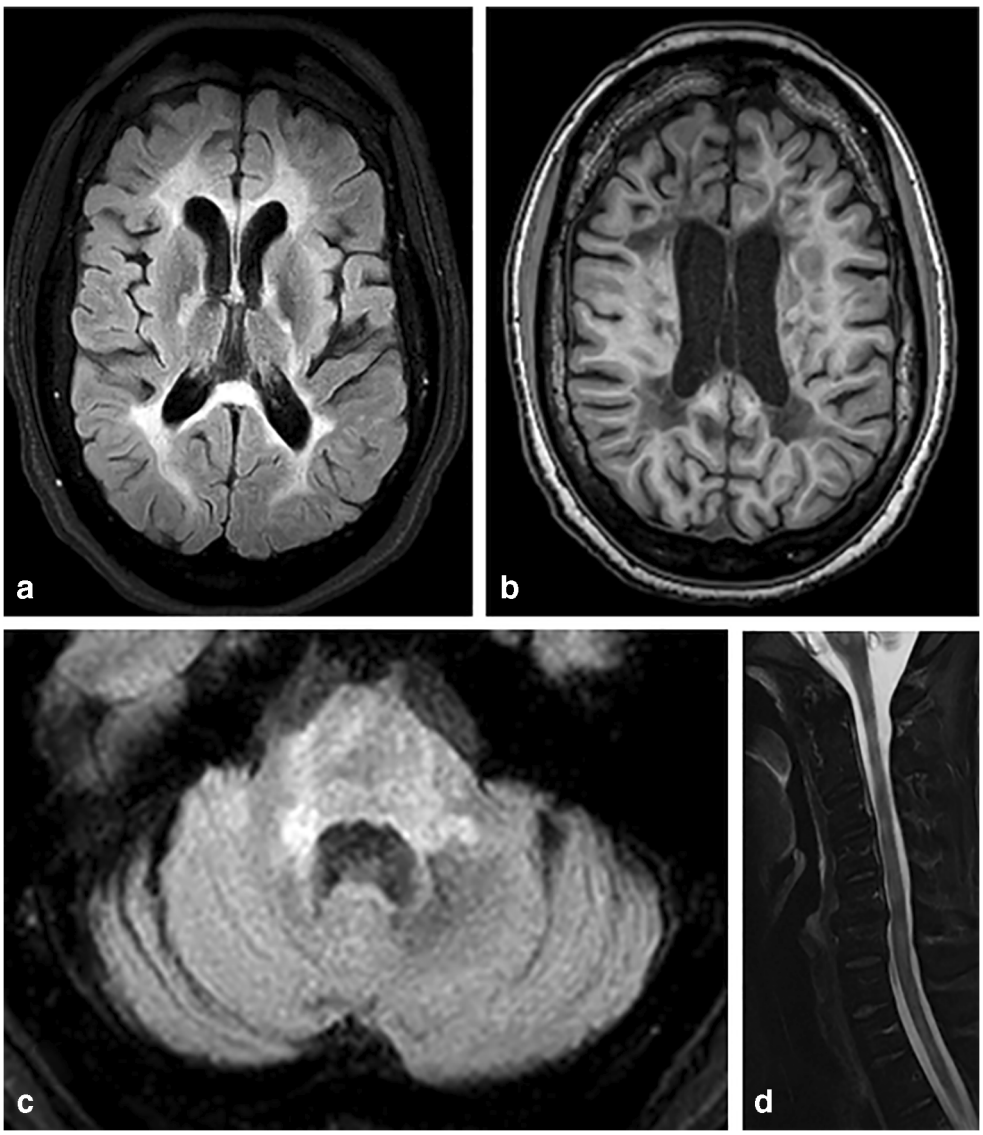

Fig. 1 MRI images of a middle-aged African-American woman with multiple sclerosis, who is wheelchair-bound and unable to independently perform any activities of daily living. **a** Extensive burden of periventricular and callosal T2/FLAIR hyperintensities, with global brain volume loss. **b** Large T1 black holes (marker of permanent damage from demyelinating lesions). **c** Extensive burden of infratentorial disease, in the pons and cerebellar peduncles (causing ataxia in this patient). **d** Patchy STIR hyperintense lesions in the cervical spinal cord

outcomes [5]; therefore, a delay to diagnosis and treatment can be harmful for patients. But the literature does not appear to bear out this theory: Khan et al. found that Caucasian Americans and African-Americans had fairly similar times from disease onset to diagnosis. Access to healthcare resources may still play a role in the outpatient setting, as diagnoses are often made in inpatient settings around the time of significant relapse. However, disease-modifying treatments are prescribed from the clinic, not from the hospital. Even underinsured patients may not be able to access care with neurologists trained to treat MS, who have experience with aggressive diseases and new advances in treatment. A retrospective cohort study showed that African-Americans with MS who used Medicaid home- and community-based services (HCBS) were less likely to utilize case management, equipment, and nursing services and more likely to participate in home-based services which are not accounted for by the discrepancy of HCBS expenditures [6]. Even with access to healthcare, the resources are not being utilized.

Further, African-Americans are more likely to distrust their doctors compared with Caucasians: one study indicates that African-Americans are less likely to trust that physicians will accurately explain what it means to participate in a research study, and more likely to believe their doctors will expose them to unnecessary risk, even after controlling for other sociodemographic variables [7]. These concerns are grounded in history: there is of course a long and disgraceful history of unethical experimentation on African-Americans, with the most widely known case being the Tuskegee Syphilis Study [8]. Although the widespread adoption of Institutional Review Boards was intended to prevent such incidents from happening again, the damage they caused is long-lasting and we as physicians need to work harder to repair therapeutic trust.

Risk Factors

Although there are known risk alleles that predispose the development of multiple sclerosis, there is also a need for environmental exposure(s) that cause one person to develop MS over another. It is difficult to study genetic risk in African-Americans, because of the large diversity in ethnic backgrounds. For example, an African-American from the Caribbean may have a widely different genetic background than an African-American from Africa. HLA-DRB1*15:01 is the most commonly described risk allele in multiple sclerosis, originally described in Northern European populations [9]. Chi et al. showed that African-Americans with HLA-DRB1*15:01 risk alleles of a European haplotype had three times the risk of developing MS compared with those on the African haplotype [10•]. A genome-wide association study (GWAS) published in 2015 by Isobe et al. found no genome-wide difference in association with risk of MS of any novel multiple sclerosis genetic variants in African-Americans [11]. Thus, there appears to be a common genetic overlap between African-Americans and Caucasians of European ancestry.

There is also an important connection between latitude and risk of developing MS. Specifically, the farther from the equator a person lives, the higher their risk of developing MS [12]. This makes a clear argument for the importance of environmental factors in the risk of developing MS. Alter et al. described a migration effect in the risk of developing MS in 1978 [13], and the effect has since been reconfirmed repeatedly. More recently, a Danish study by Nielson et al. described the risk of developing MS in people who came from low-risk countries to Denmark (which is a high-risk country). The risk of MS in someone who migrated to Denmark before the age of 15 is close to the risk in the country of origin. This is compared with someone who immigrated to Denmark after their teenage years, after which the risk is close to the risk of a Danish-born patient [14].

One theory explaining the correlation between increased risk of developing MS and residence farther from the equator is that people who live at latitudes farther from the equator get less sun exposure, and therefore less exposure to vitamin D. Caucasian patients with higher levels of serum 25-hydroxy vitamin D (25OHD) have reduced risk of developing MS [15]. The MS Sunshine study was conducted to determine if there are protective effects of 25OHD and/or sun exposure in MS risk in the African-American and Hispanic populations as compared with Caucasians [16•]. Higher serum levels of 25OHD were associated with a lower risk of MS in the Caucasian group only, although the lifetime sun exposure appears to reduce the risk of MS regardless of race and ethnicity. The association between Caucasian race and serum 25OHD may not be from the serum 25OHD level itself, but from the ultraviolet ray exposure producing more 25OHD through intradermal synthesis. Perhaps the total serum 25OHD is not an accurate reflection of bioavailable vitamin D. Further evidence comes from studies showing African-Americans express a different dominant isoform of the vitamin D transporter protein [17, 18], meaning vitamin D metabolites may not get to target cells (lymphocytes) as easily as they do in Caucasians, lowering its immunosuppressive effects.

Disease Course

African-American patients with MS can have a more aggressive disease course than Caucasian counterparts. Cree et al. studied the clinical characteristics of MS in African-Americans and found that African-Americans have greater likelihood in developing “opticospinal MS” and transverse myelitis with a more aggressive disease course, with no difference in proportion of women to men nor MS subtype [19].

Median time to diagnosis was 1 year in African-American patients compared with 2 years in Caucasian American patients, which argues a more severe symptomatology in African-Americans that leads them to seek medical attention sooner. The age of onset in African-Americans is 2.5 years later than Caucasian Americans, and it is known that late-onset multiple sclerosis can portend a poor prognosis [20]. Naismith et al. found that African-Americans with MS had a higher prevalence of cerebellar dysfunction, worse EDSS scores at diagnosis, 4- to 6-year follow-up, and final follow-up compared with their Caucasian counterparts. Disabling cerebellar signs such as ataxia is associated with less improvement with rehabilitation, requiring mobility aids such as wheelchairs and canes [21]. The tempo of the disease course is accelerated in African-American patients, evidenced by a study looking at a Multiple Sclerosis Severity Scale (MSSS), which measures the rate of disease progression (rather than baseline function). Caucasian-Americans and African-Americans had similar baseline disability scores, but there were more African-American patients in a higher MSSS grade, indicating faster progression of disability [22]. These patients need to be treated early and aggressively in order to prevent further disability [23].

Biomarkers for Disease Severity

Not only do African-American patients have higher clinical disability, biomarkers used to follow MS disease severity are affected as well (Table 1). Brain volume loss in MS has been linked to disability progression and is an important biomarker for progressive forms of MS. African-Americans with MS exhibit a more progressive neurodegenerative pattern than Caucasians with MS, especially in retinal and cerebral tissues. Studies have shown that gray matter, white matter, and thalamic nuclear atrophy rates are double in the African-American population [25•]. Axonal injury and neuronal loss leading to gray matter volume loss contribute to the overall clinical disability, independent of white matter volume loss. There have been specific patterns of cortical atrophy identified in MS patients compared with their age-matched controls as well as thalamic atrophy, which is found to occur even in the earliest stages of MS. African-Americans with MS have increased global cortical thinning even when controlling for EDSS in comparison with the Caucasian population, who tend to have more thalamic volume loss [26•]. Another study compared magnetized transfer ratios (MTR) between African-Americans and Caucasians [28•], which is a biomarker for tissue damage. MTR values in MS lesions, as well as in normal-appearing gray and white matter, were significantly lower in African-American patients, with a 31% greater T2 lesion volume and 101% greater T1 lesion volume [27].

The retina is a site of immune system activation leading to inflammation and blood-retinal barrier breakdown in multiple sclerosis. Optical coherence tomography studies have shown increased atrophy rates of the retinal nerve fiber layer and ganglion cell inner plexiform layer specifically [25•]. There is an association between MRI gray matter atrophy and ganglion cell inner plexiform layer thickness in Caucasians but not in African-American patients, arguing that even biomarkers may not be generalizable to all races [28•].

Response to Disease-Modifying Therapy

There is emerging evidence supporting the role B cells play in mediating tissue injury in MS. B cells play a contributing role with T cells in the immunopathogenesis of MS, including the production of intrathecal antibodies and cytokines, as well as their functionality as an antigen-presenting cell. Seraji-Bozorgzad et al. hypothesized that CSF IgG index may be associated with gray matter volume loss and that this would be seen significantly higher in African-Americans compared with that in Caucasian patients with MS [24••], as higher CSF IgG indices are associated with faster disease progression. They performed a cross-sectional study which showed that the gray matter brain volume was inversely related to the CSF IgG index for the entire group (both African-American and Caucasian MS populations). However, a subgroup analysis by race revealed this inverse correlation was mostly driven by the African-American patients. African-Americans in this study had statistically significant higher scores of disability, and more patients were in the secondary progressive stage of MS, which may have driven some of their results. However, these data support

Table 1 Biomarker and clinical differences in African-Americans with MS as compared with Caucasians

Biomarkers	Clinical characteristics
Higher CSF IgG index [24••]	"Opticospinal MS," transverse myelitis and cerebellar disease more common [19]
Increased rates of cortical and thalamic brain atrophy [25•, 26•, 27, 28•]	Age of onset 2.5 years later [20]
Increased rates of ganglion cell inner plexiform layer atrophy [25•, 28•]	Higher scores of clinical disability [21]
Lower serum vitamin D levels [15, 16•, 17, 18]	Accelerated rate of progression [22]

the possibility that central nervous system tissue injury may be more humorally mediated in African-Americans. The question remains how this is relevant when making treatment decisions for African-American patients, and if B cell–depleting monoclonal antibody therapies may be more beneficial in this population.

One would wonder if part of the reason for a more severe disease course in African-Americans could be due to different responses to MS treatment. In the EVIDENCE study comparing subcutaneous and intramuscular forms of interferon beta-1a, the African-American subjects had more relapses and had lower rates of NEDA (no evidence of disease progression). These data were not statistically significant, but there were trends in this small cohort of patients. The African-American patients in that study developed more new lesions on MRI ($p = 0.03$) with a sample size of 36 out of 652 total patients [29]. These data sparked debate on whether interferon therapy was less effective in African-American patients; however, it also may reflect disease severity if these patients are having more breakthrough disease activity on treatment. There were a total of 49 African-American patients in clinical trials of natalizumab, and post hoc analysis found that in this group, natalizumab reduced the annualized relapse rate over 2 years by 60% [30], when it was 68% in the total study population [31]. Natalizumab did not meet significance in decreasing clinical disability progression in African-Americans; however, this may be due to the small sample size. A post hoc study of the African-American patients in the OPERA I and OPERA II trials for ocrelizumab showed that efficacy outcomes were consistent with the overall pooled population [32]. These subgroup analyses are promising, but given the small sample sizes of African-Americans in clinical trials, it does not prove the study results to be generalizable in all races.

Conclusions

African-Americans are obviously underrepresented in clinical trials for disease-modifying drugs in MS, and it is likely due to a variety of reasons. In the BENEFIT study of interferon beta-1b, which was the first disease-modifying therapy approved for multiple sclerosis, 97.7% of patients enrolled were Caucasian [33]. All clinical trials for multiple sclerosis medications have less than 10% African-Americans, with most trials enrolling less than 5%. [34]. Trying to perform subgroup analyses of these patients in clinical trials has been attempted, but it is difficult to generalize medication efficacy to all patient groups when the medications are primarily tested in Caucasians and the subgroup sample sizes are so small. We as healthcare professionals need to make a better effort to recruit patients of all races and ethnicities for clinical trials, and pharmaceutical companies should make it a priority to have clinical trials mimic the demographics of the target population. Further, healthcare professionals should be aware that African-Americans may be distrustful of physicians and clinical trials. But rather than allowing that to bias physicians against suggesting clinical trial participation, physicians should take steps to ameliorate African-American patients' concerns and to prove that they are trustworthy caregivers. Taking all of these steps is critical, given that the incidence rate of MS is highest in black women and that the disease is more severe in African-Americans. Our duty to our patients demands nothing less.

Compliance with Ethical Standards

Conflict of Interest Sara Klein declares no potential conflicts of interest.

Veronica P. Cipriani has received honoraria from Biogen Idec, Genentech, EMD Serono, and Sanofi Genzyme for educational or consulting activities. She has received honoraria for speaking for Genentech.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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