Title
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Permalink
https://escholarship.org/uc/item/0wg1w22x

Journal
Annals of Neurology, 77(2)

ISSN
0364-5134

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Publication Date
2015-02-01

DOI
10.1002/ana.24308

Peer reviewed

Retinal Damage and Vision Loss in African-American Multiple Sclerosis Patients

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Abstract

Objective—To determine whether African-American (AA) multiple sclerosis (MS) patients exhibit more retinal damage and visual impairment compared to Caucasian-American (CA) MS patients.

Methods—687 MS patients (81 AA) and 110 healthy control (HC) subjects (14 AA) were recruited at three academic hospitals between 2008 and 2012. Using mixed effects regression models, we compared high and low contrast visual acuity (HCVA and LCVA) and high-definition spectral-domain optical coherence tomography (Cirrus-OCT) measures of retinal architecture between MS patients of self-identified AA and CA ancestry.

Results—In HC, baseline peripapillary retinal nerve fiber layer thickness (RNFL) was 6.1 µm greater in AA (p = 0.047), while ganglion cell / inner plexiform layer (GCIP) thickness did not differ by race. In MS patients, baseline RNFL did not differ by race, and GCIP was 3.98 µm thinner in AA (p = 0.004). AA had faster RNFL and GCIP thinning rates compared to CA (p = 0.004 and p= 0.046, respectively). AA MS patients had lower baseline HCVA (p = 0.02) and worse LCVA per year of disease duration (p= 0.039). Among patients with an acute optic neuritis (AON) history, AA had greater loss of HCVA than CA patients (p = 0.012).

Interpretation—This multicenter investigation provides objective evidence that AA MS patients exhibit accelerated retinal damage compared to CA MS patients. Self-identified AA ancestry is associated with worse MS-related visual disability, particularly in the context of an AON history,

suggesting a more aggressive inflammatory disease course among AA MS patients or a subpopulation therein.

Introduction

Several epidemiologic studies report that African-Americans (AA) have a lower relative risk of developing multiple sclerosis (MS) compared to Caucasian-Americans (CA).[1–4] More recent investigations have challenged this notion, as the relative risk of MS appears to be higher among African-Americans in particular populations.[5, 6] Compared to earlier risk estimates obtained from male US military veteran cohorts in the mid-20th century, the contemporary risk estimates stem from more refined ascertainment methods and may be more accurate given their derivation from populations that are more racially diversified and more inclusive of women, who comprise the majority of MS cases.

While there is renewed debate about the magnitude and direction of these relative risk estimates between racial groups, there is now less doubt that African-American MS patients tend to fare worse than their Caucasian-American counterparts. Several independent investigations show that clinical signs, inflammatory biomarkers, and MRI characteristics of MS are significantly more ominous in African-Americans. At the time of diagnosis and onward, African-Americans have higher expanded disability status scale (EDSS) scores and multiple sclerosis severity scores (MSSS).[7–10] They are also more likely to suffer from transverse myelitis (TM) and ambulatory disability.[9, 11] Markers of intrathecal immunoglobulin synthesis are seen more frequently and at higher levels than in Caucasian-Americans.[12] MR imaging reveals more severe demyelination and structural damage with greater T2 and T1 lesions volumes, as well as lower magnetization transfer ratios for lesions and normal appearing white and grey matter.[13, 14]

Retinal and visual dysfunction are common in MS patients, and if MS expresses a more aggressive phenotype in patients of African descent, then one might reasonably expect worse manifestations with respect to objective measures of retinal integrity and corresponding visual dysfunction. Perhaps contrary to expectation, African-Americans do not necessarily have a higher frequency of acute optic neuritis (AON) attacks.[11] Nonetheless, African-Americans with a history of AON do seem to have more severe vision loss both at baseline and after a year of observation as compared to Caucasian-American patients with a history of optic neuritis.[15]

In this large multi-center longitudinal study, we employed high-speed, high-definition optical coherence tomography (OCT) and visual acuity testing to investigate whether MS has a disparate impact with respect to retinal pathology and visual outcomes in African-Americans compared with Caucasian-Americans.

Methods

Study Design and Participants

Healthy control subjects and patients with MS were recruited by convenience sampling of staff and consecutive eligible patients at Johns Hopkins University (Baltimore, MD), the

University of Pennsylvania (Philadelphia, PA), and the University of Texas Southwestern (Dallas, TX) between September 2008 and December 2012. Ages ranged from 18 to 76 years. MS diagnoses were confirmed in accordance with McDonald Criteria and included relapsing-remitting (RRMS) or secondary progressive (SPMS) forms.[16, 17] Primary progressive cases were excluded, as these patients are reportedly less likely to develop visual disturbances compared with RRMS.[18] Additionally, neuromyelitis optica (NMO) and NMO Spectrum disorder patients diagnosed via 2006 Wingerchuk criteria, as well as patients with other known neuroinflammatory disorders, were excluded.[19] Healthy control subjects were also recruited from associates or family members of staff and patients at the respective centers. Patients or subjects with other known neurologic or ophthalmologic disorders, diabetes mellitus, uncontrolled hypertension, glaucoma, or refractive errors exceeding +/− six diopters were also excluded. A collaborative database of acquired optical coherence tomography measures, visual acuity measures, and demographic features of HC and MS patients was created and interrogated. Institutional Review Board approval was acquired at each institution and written informed consent was obtained from all participants prior to study enrollment.

Procedures

Retinal imaging was performed by spectral domain Cirrus HD-OCT (model 4000, software version 5.0; Carl Zeiss Meditec, Dublin, CA, USA) using a previously outlined protocol. [20, 21] Scans of the peripapillary area and maculae were acquired with the Optic Disc Cube 200 × 200 and Macular Cube 512 × 128 scanning protocols, respectively. Additionally, the Ganglion Cell Analysis (GCA) protocol was performed to quantify macular ganglion cell/inner plexiform layer (GCIP) thickness in a subset of patients (73 AA and 542 CA). OCT scans with signal strengths below 70% or artifactual anomalies were excluded. Visual acuity was assessed using standardized 100% (high contrast visual acuity, HCVA), 2.5%, and 1.25% (both considered as low contrast visual acuity, LCVA) retroilluminated Sloan letter charts with a maximum score of 70 letters (distributed as lines of five letters). Acuity assessments were performed by trained technicians involving standardized protocols outlined previously in published literature.[22]

Statistical Analyses

Statistical analyses were performed using Stata 12 (StataCorp LP, College Station, TX). The Shapiro-Wilk test was used to determine the normality of distributions. Comparisons of non-normally distributed variables between groups were done using the Wilcoxon rank-sum test. Comparisons of normally distributed variables across groups were performed using the Student's t-test. The chi-squared test was used for group comparisons of proportions (sex, race, AON history). Mixed effects linear regression analyses were undertaken for continuous responses of both OCT (i.e., retinal nerve fiber layer <RNFL> thickness, macular thickness, and GCIP) and visual acuity measures (via Sloan letter charts of varying contrast intensities). The regression models included random intercepts and were used to control for inter-eye correlations within the same subject and correlations between multiple visits for each subject. Covariates for adjustment included age at the first OCT visit, duration of disease (defined from the date of diagnosis to the time of the first clinical visit), years of follow-up, sex, race, and history of AON. AON history was labeled categorically as true/

false for the affected eye based on whether or not the patient was previously diagnosed by a physician (an ophthalmologist or neurologist). Interaction terms (race by time, and race by AON history) were used to determine the impact of race on retinal thinning and visual acuity loss. Parsing of differences by race was performed in models for RNFL and GCIP that each included interaction terms. Similarly, in visual acuity analyses, coefficients were obtained from models of acuity (at each respective contrast level) that included interaction terms. In all analyses, statistical significance was defined at a threshold of $p < 0.05$.

Results

Characteristics of the 110 control subjects and 687 MS patients, including p-values for comparisons by race within the groups, are outlined in Table 1. Among MS patients, the AA group had a lower mean age ($p = 0.03$). The proportion of AA subjects was not significantly different in both the MS and control groups ($p = 0.77$). The proportion of patients with AON was not found to differ between AA and CA patients ($p = 0.30$), and the proportion of patients receiving disease-modifying therapy did not appear to differ between CA and AA patients ($p = 0.98$).

OCT Analyses

Cross-sectional analysis at baseline (Table 2), adjusted for age and sex, suggested that the average RNFL of AA healthy control subjects was thicker compared to CA subjects in this cohort ($p = 0.047$). Regionally, all retinal quadrants appeared significantly thicker in AA compared to CA control subjects except the temporal region. Macular thickness was not significantly different between AA and CA subjects among HC. Also, there was not a significant difference in GCIP thickness among controls.

Among MS patients, however, at baseline and with adjustment for age, sex, disease duration, and history of AON, there was no significant difference in RNFL thickness between racial groups ($p = 0.31$). Regionally, temporal quadrant RNFL thickness was 4.4 μm thinner in AA patients compared to CA patients ($p = 0.017$); quadrant RNFL thickness measurements did not otherwise vary by race among MS patients. Average GCIP and overall macular thickness were significantly thinner in AA patients compared to CA patients ($p = 0.004$ and $p < 0.001$).

The rate of peripapillary RNFL thinning in healthy individuals, measured using spectral-domain OCT, has been determined as approximately 0.25 μm per year (previously reported time-domain OCT measures ranging from 0.16 to 0.20 μm per year) with no difference across racial groups.[22–24] Using interaction terms in the mixed effects regression models, we found that African-American race modifies the rate of RNFL and GCIP thinning during follow-up ($\beta = -1.2$ μm/year, $p = 0.004$ and $\beta = -0.29$ μm/year, $p = 0.046$, respectively) beyond that of CA patients who experienced a 0.31μm/year decline (Table 3 and Figure 1). In essence, AA MS patients appeared to have faster RNFL and GCIP thinning compared to CA MS patients during follow-up. Additionally, AA patients trended toward a greater loss of RNFL per year of disease duration ($p = 0.056$) and had a significantly greater loss of GCIP per year of disease duration compared to otherwise similar CA patients ($p = 0.015$).

Visual Acuity Analyses

There were no clinically significant differences in visual acuity of HC at baseline by race, sex, or age at any of the three contrast levels. Among MS patients, there were no clinically significant differences in baseline visual acuity of MS patients by sex or age at any contrast level. AA MS patients scored lower on HCVA at baseline (β = −3.5 letters, p = 0.02, 95% CI −6.6 – −0.5 letters). No such difference was observed between AA and CA MS patients at the 2.5% and 1.25% contrast levels.

Interaction terms in the mixed effects regression analysis did not show any additional decrement in visual acuity for AA patients beyond that of CA patients for HCVA (Table 4). AA patients had a greater loss of visual acuity per year of disease duration at the 2.5% and 1.25% contrast levels (p = 0.039 and p = 0.049, respectively) compared to CA patients (Table 4). Also, the impact of AON was more severe for AA patients; an interaction term showed that AA MS patients with a history of AON suffered an additional loss of five letters of HCVA beyond that of CA counterparts at any given time (β = −5.1 letters, p = 0.012). This interaction did not persist at lower contrast levels, possibly due to a floor effect precluding observation of a difference between groups at low contrast levels.[22]

Discussion

This work utilized spectral domain OCT and acuity assessments in an investigation designed to test for disparities in retinal damage and visual measures between African-American and Caucasian-American MS patients. Healthy control AA subjects appeared to have a thicker peripapillary RNFL compared to CA subjects, with most of this difference attributable to thicker superior, nasal, and inferior quadrant measures while the temporal quadrant trended toward being thinner in AA subjects. These average and regional differences are consistent with prior published literature showing overall thicker retinas in AA subjects but thinner temporal peripapillary regions. [25–27] In contrast, we found no difference in average RNFL thickness between racial categories among MS patients. The temporal quadrant, which anatomically corresponds to fibers from the papillomacular bundle, was significantly thinned in AA patients compared to CA patients. There was no difference in macular thickness by race among controls, although other studies have reported thinner macular measures in AA compared to CA subjects.[28] Among MS patients in our study, the macula was thinner in the AA group.

Perhaps the most important finding of this study is that AA MS patients appeared to have accelerated RNFL and GCIP thinning when compared to CA MS patients. The rate of retinal damage appears augmented in AA MS patients, implying that these patients may experience more visual dysfunction as time accrues. Moreover, we found more impaired vision (HCVA) at baseline in AA patients (β = −3.5 letters, p = 0.02) and a greater loss of LCVA per year of disease duration (β = −0.5 letters / year, p = 0.039 at 2.5% contrast). If this decline is approximately linear during a portion of the disease course, then AA MS patients would be expected to gradually lose visual acuity beyond that expected for otherwise similar CA MS patients. Indeed, this phenomenon is suggested by recent longitudinal analyses of outcomes by race/ethnicity in the Optic Neuritis Treatment Trial (ONTT) – AA optic neuritis patients experienced worse contrast sensitivity and visual acuity loss compared to

CA patients during the 15-year period following a first AON event.[29] These patients were initially diagnosed with AON and followed prospectively in the ONTT; additional analysis has shown that the cohort's cumulative risk of developing MS after 15 years was 50%.[30, 31] This raises the possibility that deterioration in visual function was spurred by ongoing subclinical disease activity beyond an initial AON event.

Optic neuritis events can affect the trajectory of retinal thinning and vision deterioration; in our study population, the frequency of AON did not vary between the two groups. We found that the impact of AON was more severe for AA patients compared to CA patients, resulting in an additional five letters (one line) of 100% contrast visual acuity loss at any given time (we did not see this difference at lower contrast levels, which may be attributable to a floor effect whereby mean letter acuity scores at 2.5% and 1.25% contrast were too low to observe a meaningful difference between AA and CA patients even if one were present). This is consistent with prior reports of the seemingly more aggressive nature of optic neuritis in patients of African descent, both in MS and neuromyelitis optica (NMO). In one study, it appeared that patients of African descent were more likely to have "atypical" episodes of AON requiring corticosteroid treatment, and these patients were overrepresented among those diagnosed with NMO spectrum disorder.[32] In another investigation, AA MS patients with AON more frequently had severe vision loss and worse vision after follow-up times exceeding one year; however, the study took place before the advent of widespread NMO antibody testing, and a number of the AA patients had significant concurrent spinal cord involvement.[15, 33] It is possible that NMO may have confounded interpretation of the results. Our cohort was recruited beginning in 2008, during the era of NMO antibody testing and enhanced appreciation for the scrutiny required in identifying NMO patients among those with neuroinflammatory disease. Patients for this study were clinically evaluated and diagnosed with MS as defined by McDonald criteria, while excluding those with plausible evidence of other neuroinflammatory conditions.[16, 17]

We acknowledge limitations of the study and its interpretation, as well as items that would enhance its scope, viz.: (1) AON events were analyzed categorically rather than as individual events, (2) assessment of visual function was restricted to acuity testing, and (3) the duration of disease modifying therapy (DMT) exposure across the two groups is unknown.

Regarding AON, the timing and number of optic neuritis events for each patient were not included in our analysis. Optic neuritis history was coded categorically as true or false regarding whether any episodes had ever been recorded for each individual. Although it is possible that the number of events per patient varied between the groups, we found no meaningful difference in the proportions having experienced AON. Similarly, among patients with optic neuritis and/or MS, other large studies have reported either no difference by race in terms of AON incidence (including unilateral, bilateral sequential, or bilateral simultaneous), or in some cases, higher AON incidence among CA patients.[11, 15, 30]

Regarding vision analyses, we examined contrast letter acuity, but did not include other evaluations such as systematic testing of color discrimination, visual fields, visual evoked

potentials, or electroretinography. These investigations would be informative regarding several other facets of visual system physiology.

With respect to controlling for effects of disease modifying therapy (DMT), approximately 30% of the cohort had reliable treatment data available from the outset, and the proportions of these AA and CA patients receiving DMT were similar (p = 0.98). Other epidemiologic studies have consistently shown that AA and CA MS patients who see a neurologist are equally likely to receive DMT.[7, 8, 11] While the AA and CA patients in our cohort did not differ in the proportion treated with DMT, the overall length of exposure for the individual patients and across the two groups of patients are unknown. In one study of insured MS patients within a multispecialty group practice, AA patients had lower medication possession ratios during a two-year period, raising concern that diminished adherence may be one of the factors contributing to worse outcomes.[34] However, disability measures (e.g., MSSS) in AA patients have appeared worse than CA patients notwithstanding data showing comparable DMT adherence rates across racial and ethnic categories.[10]

In addition to the recognized aspects of MS that are more ominous in AA patients – overall disability scores, the incidence of transverse myelitis, ambulatory disability, the detection of CNS inflammatory biomarkers, and MRI evidence of CNS damage – results of our study imply that vision is another domain of MS in which its manifestations appear more severe for AA patients. Inflammatory insults appear to cause greater retinal damage in AA patients, and future studies may shed light on the interplay between inflammation and neurodegenerative sequelae of MS in this patient population. Furthermore, the reports of divergent outcomes suggest that contextual sub-analyses by race and/or ethnicity should be considered when developing MS clinical trials and observational studies. Currently, it is unclear why AA MS patients experience more disabling effects of the disease, and investigations have yet to determine the extent to which environmental or genetic factors are responsible for this important disparity. For example, vitamin D insufficiency has been associated both with higher risk of developing MS and disease exacerbations; although AA patients have been shown to have lower vitamin D levels than CA patients, this difference alone has not yet been shown to account for the contrast in disease severity between the groups. [35–38] Epidemiologic studies of disparate health outcomes in MS are a necessary and valuable step toward understanding the basis of amplified disability in adversely affected populations. Progress in this area of investigation will ultimately be translated into important dividends of collaborative research efforts – the development of optimal strategies to mitigate or prevent severe disease manifestations across the broadest spectrum of MS patients.

Acknowledgments

Idec, and Novartis, and the MS Society of America. ESS, OA, AC, DC, and TCF have no relevant disclosures to report.

References

1. Kurtzke JF, Page WF. Epidemiology of multiple sclerosis in US veterans: VII.. Risk factors for MS. Neurology. 1997 Jan; 48(1):204–13. [PubMed: 9008519]

2. Kurtzke JF, Beebe GW, Norman JE Jr. Epidemiology of multiple sclerosis in U.S. veterans: 1. Race, sex, and geographic distribution. Neurology. 1979 Sep; 29(9 Pt 1):1228–35. [PubMed: 573402]

3. Poser CM. The epidemiology of multiple sclerosis: a general overview. Annals of neurology. 1994 Dec; 36(Suppl 2):S180–93. [PubMed: 7998787]

4. Poser CM, Vernant JC. Multiple sclerosis in the black population. Bulletin de la Societe de pathologie exotique (1990). 1993; 86(5 Pt 2):428–32. [PubMed: 7819795]

5. Wallin MT, Culpepper WJ, Coffman P, et al. The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service. Brain : a journal of neurology. 2012 Jun; 135(Pt 6):1778–85. [PubMed: 22628389]

6. Langer-Gould A, Brara SM, Beaber BE, Zhang JL. Incidence of multiple sclerosis in multiple racial and ethnic groups. Neurology. 2013 May 7; 80(19):1734–9. [PubMed: 23650231]

7. Naismith RT, Trinkaus K, Cross AH. Phenotype and prognosis in African-Americans with multiple sclerosis: a retrospective chart review. Multiple sclerosis. 2006 Dec; 12(6):775–81. [PubMed: 17263006]

8. Weinstock-Guttman B, Jacobs LD, Brownscheidle CM, et al. Multiple sclerosis characteristics in African American patients in the New York State Multiple Sclerosis Consortium. Multiple sclerosis. 2003 Jun; 9(3):293–8. [PubMed: 12814178]

9. Kaufman MD, Johnson SK, Moyer D, Bivens J, Norton HJ. Multiple sclerosis: severity and progression rate in African Americans compared with whites. American journal of physical medicine & rehabilitation / Association of Academic Physiatrists. 2003 Aug; 82(8):582–90. [PubMed: 12872014]

10. Kister I, Chamot E, Bacon JH, et al. Rapid disease course in African Americans with multiple sclerosis. Neurology. 2010 Jul 20; 75(3):217–23. [PubMed: 20644149]

11. Cree BA, Khan O, Bourdette D, et al. Clinical characteristics of African Americans vs Caucasian Americans with multiple sclerosis. Neurology. 2004 Dec 14; 63(11):2039–45. [PubMed: 15596747]

12. Rinker JR 2nd, Trinkaus K, Naismith RT, Cross AH. Higher IgG index found in African Americans versus Caucasians with multiple sclerosis. Neurology. 2007 Jul 3; 69(1):68–72. [PubMed: 17606883]

13. Howard J, Battaglini M, Babb JS, et al. MRI correlates of disability in African-Americans with multiple sclerosis. PloS one. 2012; 7(8):e43061. [PubMed: 22900088]

14. Weinstock-Guttman B, Ramanathan M, Hashmi K, et al. Increased tissue damage and lesion volumes in African Americans with multiple sclerosis. Neurology. 2010 Feb 16; 74(7):538–44. [PubMed: 20089944]

15. Phillips PH, Newman NJ, Lynn MJ. Optic neuritis in African Americans. Archives of neurology. 1998 Feb; 55(2):186–92. [PubMed: 9482360]

16. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Annals of neurology. 2011 Feb; 69(2):292–302. [PubMed: 21387374]

17. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Annals of neurology. 2005 Dec; 58(6):840–6. [PubMed: 16283615]

18. Stevenson VL, Miller DH, Rovaris M, et al. Primary and transitional progressive MS: a clinical and MRI cross-sectional study. Neurology. 1999 Mar 10; 52(4):839–45. [PubMed: 10078736]

19. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet neurology. 2007 Sep; 6(9):805–15.

20. Saidha S, Syc SB, Durbin MK, et al. Visual dysfunction in multiple sclerosis correlates better with optical coherence tomography derived estimates of macular ganglion cell layer thickness than

peripapillary retinal nerve fiber layer thickness. Multiple sclerosis. 2011 Dec; 17(12):1449–63. [PubMed: 21865411]

21. Saidha S, Syc SB, Ibrahim MA, et al. Primary retinal pathology in multiple sclerosis as detected by optical coherence tomography. Brain : a journal of neurology. 2011 Feb; 134(Pt 2):518–33. [PubMed: 21252110]

22. Talman LS, Bisker ER, Sackel DJ, et al. Longitudinal study of vision and retinal nerve fiber layer thickness in multiple sclerosis. Annals of neurology. 2010 Jun; 67(6):749–60. [PubMed: 20517936]

23. Budenz DL, Anderson DR, Varma R, et al. Determinants of normal retinal nerve fiber layer thickness measured by Stratus OCT. Ophthalmology. 2007 Jun; 114(6):1046–52. [PubMed: 17210181]

24. Ratchford JN, Saidha S, Sotirchos ES, et al. Active MS is associated with accelerated retinal ganglion cell/inner plexiform layer thinning. Neurology. 2013 Jan 1; 80(1):47–54. [PubMed: 23267030]

25. Girkin CA, McGwin G Jr, Sinai MJ, et al. Variation in optic nerve and macular structure with age and race with spectral-domain optical coherence tomography. Ophthalmology. 2011 Dec; 118(12): 2403–8. [PubMed: 21907415]

26. Knight OJ, Girkin CA, Budenz DL, Durbin MK, Feuer WJ. Effect of race, age, and axial length on optic nerve head parameters and retinal nerve fiber layer thickness measured by Cirrus HD-OCT. Archives of ophthalmology. 2012 Mar; 130(3):312–8. [PubMed: 22411660]

27. Girkin CA, Sample PA, Liebmann JM, et al. African Descent and Glaucoma Evaluation Study (ADAGES): II. Ancestry differences in optic disc, retinal nerve fiber layer, and macular structure in healthy subjects. Archives of ophthalmology. 2010 May; 128(5):541–50. [PubMed: 20457974]

28. Kelty PJ, Payne JF, Trivedi RH, Kelty J, Bowie EM, Burger BM. Macular thickness assessment in healthy eyes based on ethnicity using Stratus OCT optical coherence tomography. Investigative ophthalmology & visual science. 2008 Jun; 49(6):2668–72. [PubMed: 18515595]

29. Moss HE, Gao W, Balcer LJ, Joslin CE. Association of race/ethnicity with visual outcomes following acute optic neuritis: an analysis of the optic neuritis treatment trial. JAMA ophthalmology. 2014 Apr 1; 132(4):421–7. [PubMed: 24557028]

30. Optic Neuritis Study Group. The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. Archives of ophthalmology. 1991 Dec; 109(12):1673–8. [PubMed: 1841573]

31. Multiple sclerosis risk after optic neuritis: final optic neuritis treatment trial follow-up. Archives of neurology. 2008 Jun; 65(6):727–32. [PubMed: 18541792]

32. Storoni M, Pittock SJ, Weinshenker BG, Plant GT. Optic neuritis in an ethnically diverse population: higher risk of atypical cases in patients of African or African-Caribbean heritage. Journal of the neurological sciences. 2012 Jan 15; 312(1–2):21–5. [PubMed: 21920560]

33. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet. 2004 Dec 11–17; 364(9451):2106–12. [PubMed: 15589308]

34. Lafata JE, Cerghet M, Dobie E, et al. Measuring adherence and persistence to disease-modifying agents among patients with relapsing remitting multiple sclerosis. Journal of the American Pharmacists Association : JAPhA. 2008 Nov-Dec;48(6):752–7. [PubMed: 19019804]

35. Gelfand JM, Cree BA, McElroy J, et al. Vitamin D in African Americans with multiple sclerosis. Neurology. 2011 May 24; 76(21):1824–30. [PubMed: 21606454]

36. Martinelli V, Dalla Costa G, Colombo B, et al. Vitamin D levels and risk of multiple sclerosis in patients with clinically isolated syndromes. Multiple sclerosis. 2014 Feb; 20(2):147–55. [PubMed: 23836877]

37. Runia TF, Hop WC, de Rijke YB, Buljevac D, Hintzen RQ. Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis. Neurology. 2012 Jul 17; 79(3):261–6. [PubMed: 22700811]

38. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. Neurology. 2004 Jan 13; 62(1):60–5. [PubMed: 14718698]
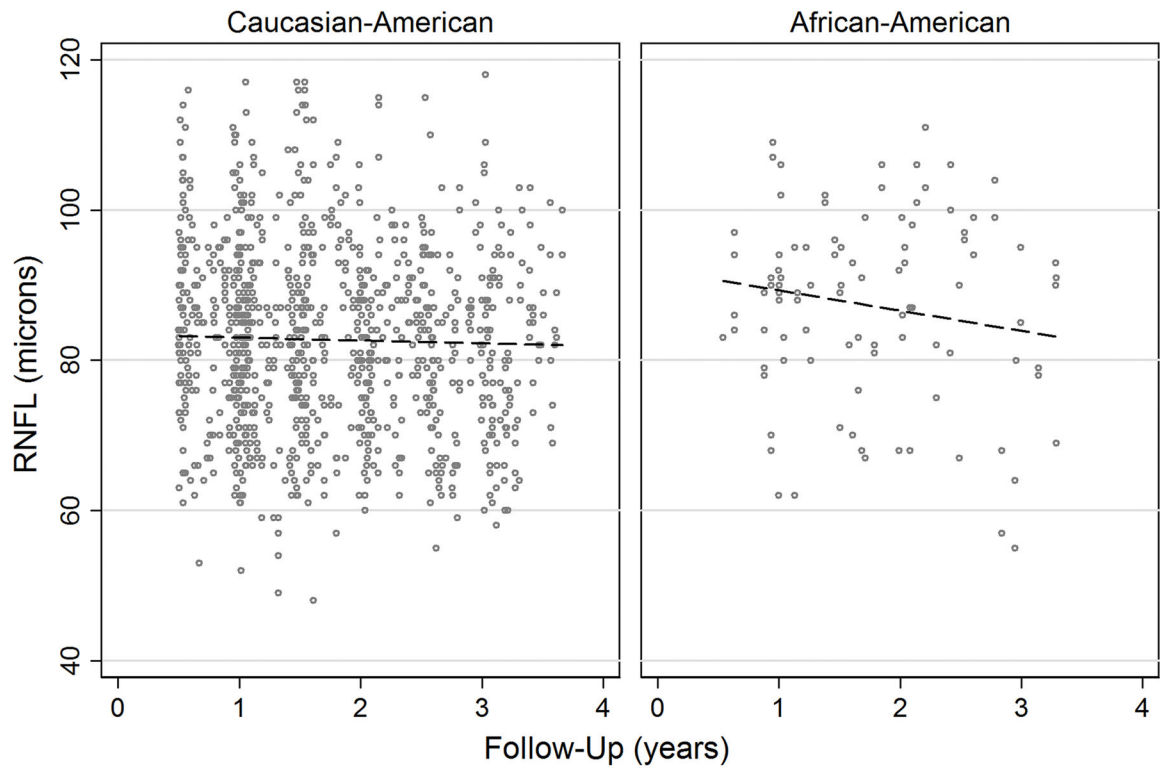
Figure 1.

Table 1

Control Subject and MS Patient Characteristics

Characteristic	Caucasian-American	African-American	p-value
Control Subjects (N = 110)			
N	96 (87%)	14 (13%)	
Baseline Age, years (mean, SD)	35 +/− 11	34 +/− 8	0.94
Sex (% Female)	60 (63%)	10 (71%)	0.51
Number of Visits (median, range)	1 (1–3)	1 (1–2)	0.71
Multiple Sclerosis Patients (N = 687)			
N	606 (88%)	81 (12%)	
Baseline Age, years (mean, SD)	44 +/− 11	41 +/− 10	0.03
Sex (N, % Female)	463 (76.4%)	63 (77.8%)	0.78
RRMS (N, %)	559 (92%)	76 (94%)	0.59
History of Acute Optic Neuritis (proportion, %)	280/598 (47%)	33/81 (41%)	0.30
Receiving disease-modifying treatment (proportion, %)	170/186 (91%)	21/23 (91%)	0.98
Disease duration, years RRMS SPMS	9.3 +/− 7.9 8.4+/− 7.3 18.4 +/−8.5	7.4 +/− 5.9 6.8 +/− 4.8 23 +/− 11.3	0.19
Baseline EDSS (median, range)	2.0, 1.0 – 6.5	2.25, 1.0 – 6.5	0.22
Visits (median, range)	3 (2–11)	3 (2–8)	0.74
Follow-up, years (median, range)	2.0 (0.5 – 3.7)	2.0 (0.6–3.3)	0.17

Table 2

Baseline Cross-Sectional Regression Analyses of RNFL, GCIP, and Macular Thickness in Healthy Controls and MS Patients

Healthy controls: African-American subjects compared to Caucasian-American subjects[1]				
OCT measure	Mean (μm)	Beta (μm)	p-value	95% CI
Average RNFL (μm)	100	6.1	0.047	0.1 – 12.1
Temporal quadrant (μm)	67	–5.2	0.092	–11.3 – 0.9
Superior quadrant (μm)	126	10.2	0.024	1.3 – 19.2
Nasal quadrant (μm)	73	8.1	0.023	1.1 – 15.2
Inferior quadrant (μm)	135	11.1	0.048	0.1 – 22.1
Average GCIP (μm)	88.6	0.44	0.872	–4.87 – 5.75
Macular Thickness (μm)	284	–3.1	0.395	–10.1 – 4.0
MS Patients: African-American patients compared to Caucasian-American patients[2]				
Average RNFL (μm)	92	–1.7	0.310	–5.1 – 1.6
Temporal (μm)	56	–4.4	0.017	–7.9 – –0.8
Superior (μm)	120	0.7	0.795	–4.4 – 5.7
Nasal (μm)	70	–1.9	0.268	–5.3 – 1.5
Inferior (μm)	123	–1.3	0.649	–6.9 – 4.2
Average GCIP (μm)	76.1	–3.98	0.004	–6.72 – –1.24
Macular Thickness (μm)	283	–11.7	<0.001	–16.4 – –7.0

[1] Analyses for Healthy Controls are adjusted for age and sex

[2] Analyses for MS Patients are adjusted for age, sex, disease duration, and history of acute optic neuritis

Table 3

Mixed effects regression of RNFL and GCIP thickness for MS patients by race[1]

	Covariate	Beta (thickness per unit time, µm/year)	p-value	95%CI
Peripapillary retinal nerve fiber layer (RNFL)	Follow-up, CA patients (µm/year)	−0.31	0.005	−0.53 – −0.10
	Race x Follow-up (interaction term for AA patients, µm/year)	−1.2	0.004	−2.0 – −0.39
	Disease duration, CA patients (µm/year)	−0.22	0.08	−0.47 – 0.03
	Race x Disease duration (interaction term for AA patients, µm/year)	−1.1	0.056	−2.2 – 0.03
Ganglion cell / inner plexiform layer (GCIP)	Follow-up, CA patients (µm/year)	−0.34	<0.001	−0.43 – −0.26
	Race x Follow-up (interaction term for AA patients, µm/year)	−0.29	0.046	−0.58 – −0.03
	Disease duration, CA patients (µm/year)	−0.29	0.010	−0.51 – −0.07
	Race x Disease duration (interaction term for AA patients, µm/year)	−1.03	0.015	−1.85 – −0.20

[1] Adjusted for age, sex, race, elapsed time (either follow-up during study, or disease duration since diagnosis), and history of acute optic neuritis. Coefficients were determined in models for RNFL and GCIP, respectively, that included interaction terms and used CA as the reference population.

Table 4

Mixed effects regression of visual acuity at varying contrast levels for MS patients by race[1]

Sloan Chart Contrast Level	Covariate	Beta	p-value	95% CI
High Contrast Visual Acuity, 100%				
	Follow-up, CA patients (β = letters/year)	**−0.5**	**0.009**	**−0.9 − −0.1**
	Race x Follow-up, (interaction term for AA patients, β= letters/year)	−0.9	0.159	−2.2 − 0.40
	Disease duration, CA patients (β = letters/year)	**−0.16**	**0.020**	**−0.3 − −0.03**
	Race x Disease duration (interaction term for AA patients, β = letters/year)	−0.2	0.347	−0.63 − 0.22
	History of AON, CA patients (β = letters)	**−2.5**	**0.001**	**−3.9 − −1.0**
	Race x History of AON, (interaction term for AA patients, β = letters)	**−5.1**	**0.012**	**−9.0 − −1.1**
Low Contrast Visual Acuity, 2.5%				
	Follow-up, CA patients (β = letters/year)	**−1.1**	**< 0.001**	**−1.5 − −0.7**
	Race x Follow-up, (interaction term for AA patients, β = letters/year)	−0.6	0.400	−1.9 − 0.7
	Disease duration, CA patients (β = letters/year)	**−0.2**	**0.020**	**−0.3 − −0.03**
	Race x Disease duration (interaction term for AA patients, β = letters/year)	**−0.5**	**0.039**	**−0.9 − −0.03**
	History of AON, CA patients (β = letters)	**−5.5**	**< 0.001**	**−7.1 − −4.0**
	Race x History of AON, (interaction term for AA patients, β= letters)	−1.7	0.432	−6.0 − 2.6
Low Contrast Visual Acuity, 1.25%				
	Follow-up, CA patients (β = letters/year)	−0.2	0.320	−0.5 − 0.2
	Race x Follow-up, (interaction term for AA patients, β = letters/year)	0.3	0.541	−0.8 − 1.5
	Disease duration, CA patients (β = letters/year)	**−0.2**	**0.003**	**−0.3 − −0.1**
	Race x Disease duration (interaction term for AA patients, β = letters/year)	**−0.4**	**0.049**	**−0.9 − −0.002**
	History of AON, CA patients (β = letters)	**−5.0**	**< 0.001**	**−6.2 − −3.6**
	Race x History of AON, (interaction term for AA patients, β = letters)	−0.1	0.950	−3.7 − 3.4

[1] Adjusted for age, sex, race, elapsed time (either follow-up during study, or disease duration since diagnosis), and history of acute optic neuritis (AON). Coefficients were determined in models of acuity at respective contrast levels that included interaction terms and used CA as the reference population.