Association of Race/Ethnicity With Visual Outcomes Following Acute Optic Neuritis
An Analysis of the Optic Neuritis Treatment Trial

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IMPORTANCE Retrospective studies have demonstrated disparate outcomes following acute optic neuritis in individuals of African descent compared with individuals of white race/ethnicity. However, published analyses of the prospectively collected Optic Neuritis Treatment Trial (ONTT) data identified no association between worse visual outcomes and black race/ethnicity.

OBJECTIVES To investigate the associations of age, sex, and race/ethnicity with visual outcomes following acute optic neuritis through application of longitudinal data analysis techniques to the ONTT data set.

DESIGN Secondary analysis of the ONTT (a prospective randomized controlled trial) data set. Our models included effects of treatment (placebo, oral prednisone, or intravenous methylprednisolone), time, and treatment × time interaction, as well as demographic covariates of age, sex, and race/ethnicity.

SETTING AND PARTICIPANTS The ONTT data were collected at multiple centers in the United States. Patients of black (n = 58) and white (n = 388) race/ethnicity with acute optic neuritis who enrolled in the ONTT within 8 days of symptom onset were included in analyses.

MAIN OUTCOMES AND MEASURES The contrast sensitivity and visual acuity (logMAR) in the affected eye were modeled using 2-stage mixed-effects regression techniques. All available follow-up data from baseline to 15 to 18 years were included.

RESULTS The data identified no relationship of age, sex, or treatment with contrast sensitivity or visual acuity outcomes. Race/ethnicity was significantly related to contrast sensitivity (P < .001) and visual acuity (P < .001) during a 15-year period following acute optic neuritis, with black race/ethnicity being associated with worse scores for both.

CONCLUSIONS AND RELEVANCE Race/ethnicity seems to be associated with contrast sensitivity and visual acuity outcomes in affected eyes following acute optic neuritis. To our knowledge, this is the largest cohort of black race/ethnicity with acute optic neuritis to be studied and represents the first evidence from a prospectively collected data set to support a hypothesis of race/ethnicity–dependent visual outcomes of acute optic neuritis.
Although most individuals recover excellent vision after acute optic neuritis, some affected patients have poor visual recovery that limits independence and reduces quality of life. Current management strategies based on population studies do not account for this outcome heterogeneity. Improved understanding of prognostic factors is necessary to tailor treatment of this potentially blinding condition. In the landmark Optic Neuritis Treatment Trial (ONTT), 7% of participants had vision worse than 20/50 after 1 year, and 3% had vision worse than 20/200 after 1 year. Age and baseline visual acuity (VA) were significantly associated with visual outcomes at 6 months. In this prospective randomized treatment trial, race/ethnicity was not associated with visual outcomes using cross-sectional analysis techniques at 6 months, 5 years, 10 years, and 15 years after acute optic neuritis. However, in a retrospective case series of optic neuritis from 2 hospitals in Atlanta, Georgia, patients of black race/ethnicity (n = 33) had worse visual outcomes than patients of white race/ethnicity (n = 63), with 36% of black patients having VA less than 20/50 and 18% less than 20/200 compared with 8% and 5% of white patients, respectively, at 1 year. In a small retrospective study of black individuals with optic neuritis in South Africa, 9 of 10 patients had VA less than 20/200 at the last follow-up visit, suggesting that poor visual outcomes among those of black race/ethnicity may be a global phenomenon.

One possible explanation for the lack of an association between race/ethnicity and visual outcomes in the ONTT is the sensitivity of the analysis techniques used. Cross-sectional visual outcomes were compared at each time point in the study; however, these do not capture change over time in individuals. Longitudinal data analysis techniques are more efficient than cross-sectional analyses because they model individual changes and differences between groups and are less susceptible to missing data. We sought to further investigate demographic associations with visual outcomes following acute optic neuritis through application of longitudinal data analysis techniques to the ONTT data set to test the hypothesis that visual outcomes following acute optic neuritis are associated with race/ethnicity.

Methods

We performed a longitudinal analysis of the prospectively collected data set from the North American ONTT (http://lions.jaeb.org/). Our study of these publicly available, existing data recorded such that participants cannot be identified was exempt from institutional review board review under US Department of Health and Human Services regulations. Full study details are provided elsewhere. Briefly, 457 individuals enrolled who manifested a first episode of acute optic neuritis in an affected eye. Major trial inclusion criteria were age 18 to 45 years and clinical examination findings consistent with unilateral acute optic neuritis, with symptoms starting within 8 days before enrollment. Major exclusion criteria were a prior episode of acute optic neuritis in the affected eye and evidence of systemic disease, other than multiple sclerosis (MS), that can be associated with acute optic neuritis. The institutional review board at each of 15 clinical centers approved the study, and participants signed an informed consent form before enrollment. Participants were randomized to 1 of 3 treatment arms (placebo, oral prednisone, or intravenous methylprednisolone) and were followed up for visual outcomes and the development of MS. The primary visual outcome was contrast sensitivity (CS), measured using Pelli-Robson chart steps (range, 0-16 triplets of letters correctly identified, where 16 is best). Secondary visual outcomes included VA, measured with Snellen retroilluminated Early Treatment of Diabetic Retinopathy Study charts and converted to logMAR (0 is equivalent to 20/20, <0 is better, and >0 is worse). Demographic variables of age, sex, and race/ethnicity (white, black, Asian, or Hispanic) were recorded based on self-report. Follow-up visits occurred 8 times in the first year and then annually through 10 years, with a final follow-up visit at 15 to 18 years. In total, 438 individuals (95.8%) completed the 6-month examination, which was the primary end point. Subsequent published analyses were based on follow-up periods of 5 to 8 years (397 individuals [86.9% retention]), 10 to 14 years (319 individuals [69.8% retention]), and 15 to 18 years (294 individuals [64.3% retention]).

Data on ONTT participants of black and white races/ethnicities were included in our analysis. Demographic and clinical factors were compared between groups using 2-sample t test, Mann-Whitney test, and χ² test. The CS and VA were modeled as continuous outcomes using mixed-effects linear models. All available follow-up data were included. Time was represented by visit number to discriminate early change in visual outcomes typical of acute optic neuritis. Multiple models were run, with different sets of potential confounders, to explore effects of treatment, time, age, sex, and race/ethnicity on visual outcomes following acute optic neuritis. Pairs of significant variables were multiplied at each time point to generate interaction variables. These were included as terms in the models to explore combined effects of potential confounders. Models were calculated for follow-up periods (0-8 years, 0 to 10-14 years, and 0 to 15-18 years) to determine the effect of declining sample size on model precision. Models were analyzed using statistical software (SAS version 9.2; SAS Institute Inc). P < .05 was considered significant.

Results

In total, 58 individuals of black race/ethnicity and 388 individuals of white race/ethnicity from the ONTT database met the criteria for analysis (Table 1). Individuals of other races/ethnicities (7 Asian and 2 Hispanic) and 2 persons found to have compressive optic neuropathies were excluded. Individuals in the black and white groups with follow-up periods of 5 to 8 years did not differ from the group members without follow-up periods of 5 to 8 years with regard to age, sex, or baseline VA (eTable in the Supplement). White patients with follow-up periods of 10 to 14 years (P = .02) and 15 to 18 years (P = .046) were older than those without follow-up data (t test for independent samples). Black patients with follow-up periods of 10 to 14 years did not differ from those without fol-
low-up data. Black patients with follow-up periods of 15 to 18 years were younger than those without follow-up data ($P = .04$, $t$ test for independent samples). Individuals lost to follow-up data at 10 to 14 years had worse baseline VA than those having follow-up data ($P = .03$, $t$ test for independent samples). This difference was not significant within race/ethnicity groups and was not observed at the follow-up period of 15 to 18 years.

A 2-stage model (with different time coefficients for visits 1-4 [stage 0] and visits 4-17 [stage 1]) provided the best fit for both CS and VA outcomes, with transition from time-dependent (ie, improving) to time-independent (ie, stable) outcomes at visit 4 (7 weeks) (Figure 1 and Figure 2). Model results for maximum follow-up periods of 15 to 18 years and 8-year follow-up time were statistically identical, although the 8-year follow-up models had greater precision in coefficient estimates because of larger sample sizes at the later time points.

We chose to present the models with up to 8 years (15 visits) of follow-up data for this reason.

The simplest model of CS did not identify a relationship between CS and treatment, treatment stage, or treatment × time interaction (Table 2, model 1). The data identified no relationship between CS and age ($P = .27$) or sex ($P = .19$). Race/ethnicity was significantly related to CS ($P = .009$), with black race/ethnicity being associated with worse (lower) scores (Table 2, model 2). The race/ethnicity effect persisted in a model that incorporated age, sex, and race/ethnicity ($P = .005$) (Table 2, model 3). No significant interaction effects were observed for race/ethnicity × treatment (Table 2, model 4), which means that the association between race/ethnicity and CS did not vary for different treatments (Table 2, model 4). Significant interactions were identified for intravenous treatment × time ($P = .04$), race/ethnicity × time ($P < .001$), and race/ethnicity × age ($P < .001$).
ethnicity × treatment stage (P < .001) (Table 2, model 5), which means that the associations between race/ethnicity and CS were different according to time and treatment stage (Table 2, model 5, and Figure 1).

The simplest model of VA identified no relationship between VA and treatment or treatment × time interaction (Table 3, model 1). The data identified no relationship between VA and age (P = .77) or sex (P = .87). Race/ethnicity was significantly related to VA (P = .03), with black race/ethnicity being associated with worse (higher) VA (Table 3, model 2). The race/ethnicity effect persisted in a model that incorporated age, sex, and race/ethnicity (Table 3, model 3). No significant interaction effects were observed for race/ethnicity and treatment (Table 3, model 4). Significant inter-

Table 2. Mixed-Effects 2-Stage Linear Models of Contrast Sensitivity From 0 to 8 Years Following Acute Optic Neuritis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (95% CI)</th>
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<tbody>
<tr>
<td>Time, visits 1–4</td>
<td></td>
</tr>
<tr>
<td>Stage, 0 is visits 1–4, 1 is visits ≥5</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
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<tr>
<td>Treatment Interactions</td>
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<tr>
<td>Age, Sex, and Race/Ethnicity</td>
<td></td>
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<tr>
<td>Race/Ethnicity × Treatment Interaction</td>
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<tr>
<td>Time and Stage Interactions</td>
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</tbody>
</table>

Abbreviations: ellipsis, not applicable; IV, intravenous; PO, by mouth.

* Each cell contains the coefficient estimate indicating the amount contrast sensitivity improves (by triplet steps) for each increment in variable (95% CI).

P < .001.

P < .01.

Figure 2. Final Model of Visual Acuity vs Time
actions were identified between intravenous treatment and time \((P = .04)\), race/ethnicity and time \((P < .001)\), and race/ethnicity and treatment stage \((P < .001)\) (Table 3, model 5, and Figure 2).

**Discussion**

The ONTT is a landmark study in neuro-ophthalmology, hailed for its prospective nature, high enrollment, and excellent follow-up data. From it, we have learned much about visual outcomes following acute optic neuritis and the association with MS. A conflict exists between published analyses\(^3-5\) of the ONTT and a retrospective study\(^6\) regarding demographic associations with acute optic neuritis visual outcomes, particularly with regard to race/ethnicity. We applied longitudinal data analysis techniques to the ONTT data set to further define demographic associations and identified a statistically significant association between black race/ethnicity and visual outcomes. Strengths of our analysis include (1) the use of a prospectively collected data set, which is less prone to selection bias than retrospective data; (2) a data set containing the largest cohort of black participants that has been reported for acute optic neuritis; and (3) the use of efficient, longitudinal analysis statistical techniques.

Black race/ethnicity seems to be associated with worse CS and VA outcomes in the affected eye from 0 to 15 years following acute optic neuritis. Black participants had worse vision at baseline as demonstrated by a significant race/ethnicity term in the models. The trajectory of vision is associated with race/ethnicity during the early recovery period such that black individuals recovered vision faster. This is demonstrated by the significance of the race/ethnicity × time interaction in the models. Although black patients had worse vision at onset and recovered at a faster rate than white patients, our models of the ONTT data set demonstrate that their final vision remained worse than that of white patients. The magnitude of the effect is within the range of significant changes based on the variability of the Pelli-Robson test\(^10\) and is clinically significant because of correlations between CS and vision-associated quality of life. No differential treatment response was associated with race/ethnicity for the acute treatments studied (ie, the race/ethnicity × treatment interaction was not significant in the models). The reasons for the race/ethnicity associations with visual function both at the time of acute optic neuritis

<table>
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<tr>
<th>Table 3. Mixed-Effects 2-Stage Linear Models of Visual Acuity From 0 to 8 Years Following Acute Optic Neuritis(^a)</th>
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<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Time, visits 1-4</td>
</tr>
<tr>
<td>Stage, 0 is visits 1-4, 1 is visits 5</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
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<tr>
<td>IV vs placebo</td>
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<tr>
<td>PO vs placebo</td>
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<tr>
<td><strong>Treatment Interactions</strong></td>
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<tr>
<td>Treatment × time, IV vs placebo</td>
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<td>Treatment × time, PO vs placebo</td>
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<td><strong>Age, Sex, and Race/Ethnicity</strong></td>
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<tr>
<td>Race/ethnicity, black is 1, white is 0</td>
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<tr>
<td>Sex, female is 1, male is 0</td>
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<tr>
<td>Age, y</td>
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<td>Treatment × sex</td>
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</tbody>
</table>

Abbreviations: ellipsis, not applicable; IV, intravenous; PO, by mouth.

\(^a\) Each cell contains the coefficient estimate indicating the amount visual acuity worsens for each increment in variable (95% CI).

\(^b\) \(P < .001\).

\(^c\) Indicates interaction term between 2 variables.

\(^d\) \(P < .05\).
diagnosis and during long-term follow-up periods are unknown. Possibilities include biological differences in disease, as well as sociocultural variations such as health care-seeking behavior,11,12 or differences in health care access and barriers. Further study is necessary to determine the relative contributions of each and the appropriate interventions to improve outcomes in all racial/ethnic groups.

We attribute our statistically significant differences in visual outcomes according to race/ethnicity for which the initial ONTT analysis did not find differences to the use of more efficient data analysis techniques. In addition to the new finding regarding a race/ethnicity association with visual outcomes, our longitudinal analysis confirms previous conclusions from the primary ONTT analyses.1,2 We found expected associations with time and with treatment × time interaction. Our models show linear improvement in vision as a function of time until visit 4 (7 weeks), with a plateau following this, as well as differences in the vision and time relationship depending on treatment. We found no association between age and visual outcomes, which was reported in cross-sectional analyses of the 6-month ONTT outcomes but not at the follow-up periods of 5, 10, or 15 years.3-5 This illustrates the value of longitudinal analysis to capture overall trends. We also found no association with sex, which is in line with prior ONTT analyses.3-5

Although our analysis supports the hypothesis of a race/ethnicity association with acute optic neuritis visual outcomes proposed by a retrospective study,6 this does not account for the difference in the proportions of individuals of black race/ethnicity with poor vision at 1 year in the ONTT (3% with worse than 20/200 at 1 year) vs in the Atlanta case series (18% with worse than 20/200 at 1 year).6 This may reflect differences in patient selection between the 2 studies, emphasizing the complementary roles for randomized trials and observational cohorts in studying the epidemiology of visual outcomes. Both the case series and the prospective randomized study are likely to have selection bias because of differences in eye care-seeking behavior based on insurance, socioeconomic status, race/ethnicity, and severity of symptoms, and this likely also affects the follow-up data.11,12 Furthermore, a degree of selection bias probably exists in the ONTT because of the tendency for minorities to be underrepresented in clinical trials.13 The ONTT prospective data set does not capture potential covariates such as socioeconomic status and insurance coverage. The Atlanta case series6 captured this in a preliminary manner by comparing African American patients from an inner-city hospital with those from a tertiary referral practice and showed no difference in vision at presentation or after 1 follow-up year between sites. However, insurance coverage and socioeconomic status at an individual patient level were not analyzed. Further study is necessary to determine if these variables have a confounding role in the association between race/ethnicity and acute optic neuritis visual outcomes.

Demyelinating disease is another important outcome following optic neuritis. Retrospective studies6,14 have demonstrated associations between race/ethnicity and the development of neuromyelitis optica (NMO) but not MS. This distinction is important given evidence that NMO-associated optic neuritis is associated with worse visual outcomes,15 manifests greater optic nerve injury,16 and may respond differentially to treatment.17 The retrospective case series6 from Atlanta that demonstrated worse visual outcomes after optic neuritis in African American patients also suggested racial/ethnic disparity in the development of NMO following optic neuritis. In total, 21% and 15% of black patients developed NMO and MS, respectively, following optic neuritis compared with 5% and 15% of white patients, respectively. However, this analysis was performed before updated NMO diagnostic criteria18 and did not report aquaporin 4 testing. A British study14 of 64 patients with optic neuritis found that 33% of African heritage individuals vs 10% of white individuals had optic neuritis associated with a corticosteroid-requiring condition such as NMO, the diagnosis of which was based on positive serum testing results for aquaporin 4 antibodies. Neuromyelitis optica has emerged as a distinct demyelinating disease since the inception of the ONTT and was not captured as distinct from MS in this trial. Therefore, we were unable to extend our analysis to this important question.

Limitations of our study include definition of race/ethnicity by self-report. While self-report of race/ethnicity has demonstrated an association with predominant genetic ancestry in multiple studies,15,20 it is generally not associated with genetic admixture, a potentially important variable. In addition, we did not analyze other potentially important demographic variables such as socioeconomic status and insurance coverage because these were not included in the ONTT data set. Another limitation is the use of an older data set, although we believe that the ONTT is still relevant because it remains the landmark and most recent study regarding treatment of optic neuritis, and treatment patterns have not changed in the interim.

Conclusions

Through application of longitudinal data analysis techniques to the ONTT, we found that race/ethnicity is associated with CS and VA outcomes in the affected eye at all time points up to 15 years following optic neuritis. To our knowledge, this is largest cohort of individuals of black race/ethnicity with acute optic neuritis to be studied and represents the first evidence from a prospectively collected data set to support a hypothesis of race/ethnicity-dependent visual outcomes of acute optic neuritis. These results have implications for understanding prognostic determinants of optic neuritis outcomes.

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Drafting of the manuscript: Moss. Critical revision of the manuscript for important intellectual content: All authors.

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REFERENCES