Diffusion Tensor Imaging in Acute Optic Neuropathies

Predictor of Clinical Outcomes

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Objective: To evaluate directional diffusivities within the optic nerve in a first event of acute optic neuritis to determine whether decreased axial diffusivity (AD) would predict 6-month visual outcome and optic nerve integrity measures.

Design: Cohort study.

Setting: Academic multiple sclerosis center.

Patients: Referred sample of 25 individuals who presented within 31 days after acute visual symptoms consistent with optic neuritis. Visits were scheduled at baseline, 2 weeks, and 1, 3, 6, and 12 months.

Main Outcome Measures: Visual acuity, contrast sensitivity, visual evoked potentials (VEPs), and thickness of the retinal nerve fiber layer (RNFL).

Results: An incomplete 6-month visual recovery was associated with a lower baseline AD (1.50 µm²/ms [95% confidence interval {CI}, 1.36-1.64 µm²/ms for incomplete recovery vs 1.75 µm²/ms [95% CI, 1.67-1.83 µm²/ms] for complete recovery). Odds of complete recovery decreased by 53% (95% CI, 27%-70%) for every 0.1-unit decrease in baseline AD. A lower baseline AD correlated with worse 6-month visual outcomes in visual acuity (r = 0.40, P = .03), contrast sensitivity (r = 0.41, P = .02), VEP amplitude (r = 0.55, P < .01), VEP latency (r = -0.38, P = .04), and RNFL thickness (r = 0.53, P = .02). Radial diffusivity increased between months 1 and 3 to become higher in those with incomplete recovery at 12 months than in those with complete recovery (1.45 µm²/ms [95% CI, 1.31-1.59 µm²/ms] vs 1.19 µm²/ms [95% CI, 1.10-1.28 µm²/ms]).

Conclusions: Decreased AD in acute optic neuritis was associated with a worse 6-month visual outcome and correlated with VEP and RNFL measures of axon and myelin injury. Axial diffusivity may serve as a marker of axon injury in acute white matter injury.

STUDY PROTOCOL AND ENROLLMENT

All subjects provided informed consent, after approval by the Washington University Human Research Protection Office and institutional review board. Six optic nerve MRI scans were obtained over the course of 12 months for all subjects aged 18 to 60 years who presented with acute visual loss consistent with a first demyelinating event of optic neuritis. A baseline MRI scan was performed within 31 days of onset of clinical optic neuritis, first characterized by symptoms of pain, loss of visual acuity, and/or loss of color vision. Study entry within the acute period necessitated enrollment before formal diagnosis was finalized. Study visits were scheduled 2 weeks after the baseline assessment and at 1, 3, 6, and 12 months. All visits included an MRI scan and clinical measures of vision. Optical coherence tomography was performed, and VEPs were obtained, at baseline, 6 months, and 12 months.

Twenty-nine subjects were enrolled, of whom 25 had at least 6 months of follow-up. Three subjects were lost to follow-up before 6 months, and 1 subject did not fit in the MRI scanner. For our study, outcome was defined at 6 months based on a return to normal vision (ie, complete recovery: a visual acuity of ≥0.8, based on the resolution adopted by the International Council of Ophthalmology, and a contrast sensitivity of >1.60 logMAR), based on the Pelli-Robson contrast sensitivity test or incomplete recovery. Twenty-three optic nerves from 21 subjects were also available for 12-month follow-up, but that included 4 optic nerves that were not usable owing to recurrent optic neuritis between months 6 and 12. Thus, 19 eyes were clinically stable enough to evaluate the durability of the outcome across 6 and 12 months. No reclassification of outcome based on visual acuity occurred between 6 and 12 months, and no eye improved by more than 1 line on the Snellen chart. Only 1 of 19 eyes (5.3%) improved to be reclassified based on the Pelli-Robson contrast sensitivity chart between 6 and 12 months. Visual stability between 6 and 12 months was also observed in the Optic Neuritis Treatment Trial.

Thus, the 6-month outcome was used to allow inclusion of data from all 31 optic nerves and to avoid potential inconsistencies from recurrent optic neuritis. The 12-month data were used for those without recurrent optic neuritis to illustrate the longitudinal changes over the year.

MRI PROTOCOL AND REGION-OF-INTEREST ANALYSIS

The optic nerve imaging protocol and analysis have been previously published. A 4-element surface receiver coil was used with a single-shot, spin-echo, echo planar imaging sequence and a 3-T MRI scanner (Allegra; Siemens AG, Munich, Germany). Eight averages utilized 12 diffusion encoding directions (b=0.60 s/mm²) and a 1.3 × 1.3 × 1.3 mm³ isotropic voxel. The region of interest was manually selected on the b0 image to include 15 to 20 consecutive voxels (9.75-13.0 mm in length, with a voxel output size of 0.65 mm³ isotropic) within the nerve center, starting 12 to 15 voxels (about 8.0 mm) posterior to the retina. To ensure reliable DTI measurements, selected voxels had a signal-to-noise ratio of at least 32, as previously described elsewhere.

CLINICAL MEASURES

Vision tests were measured by use of a 20-foot Snellen wall chart for visual acuity, a 5% contrast sensitivity chart in an illuminated cabinet at 3 m (Precision Vision, La Salle, IL), and a Pelli-Robson contrast sensitivity chart at 1 m (Metropia Ltd, Cambridg, England). Best-corrected vision was achieved with glasses or pinhole occluder. Pattern VEPs were obtained on either a Nicolet Viking Select system (CareFusion, San Diego, California) or a Diagnosys Espion system with 60-minute check size (Lowell, Massachusetts). P100 latency and N75:P100 amplitude were read in blinded fashion. If the waveform was unobtainable from inadequate vision, the maximal latency of 170 milliseconds and the minimal amplitude of 1.5 mV were used (occurring at follow-up for only 2 eyes within a single individual, at both 6 and 12 months). Optical coherence tomography RNFL thickness was obtained on a Zeiss Stratus OCT III with version 4.0 software (Henningsdorf, Germany) by a trained and certified technician, using fast RNFL scan mode. Optical coherence tomography scans with a signal strength of less than 7 were excluded.

STATISTICS

All tests were 2-tailed, and models were checked for proper covariance structure (SAS Institute, Cary, North Carolina). Spearman correlation coefficients were used to express the relationship between DTI parameters, baseline clinical measures, and 6-month clinical measures. Generalized estimating equations were used to account for repeated longitudinal measures and clustered observations from 2 eyes within an individual. Linear regression models were used to determine the effect of DTI parameters on predicting contrast sensitivity outcome, while controlling for age, sex, use of intravenous glucocorticoids, and visual acuity at onset. Logistic regression models were used to evaluate the risk of not recovering to normal vision (ie, a visual acuity of ≥0.8 and a contrast sensitivity of >1.60 logMAR), while also controlling for baseline variables as in the linear models. Linear repeated-measures models were used to determine the time course of DTI alterations, along with 95% confidence intervals (CIs).

RESULTS

DEMOGRAPHICS

Twenty-five subjects, all of whom had at least 6 months of follow-up, contributed 31 acutely injured optic nerves (Table 1). Three subjects presented with simultaneous and bilateral optic neuritis, and another 3 subjects had sequential optic neuritis, with the onset of optic neuritis occurring in the second eye within 21 days of it occurring in the first eye. In all sequential cases, the second eye had been clinically and radiographically documented as normal at the time the first eye was affected. Fifteen subjects presented with clinically isolated syndrome (optic neuritis with an abnormal brain MRI consistent with demyelination), 5 had isolated optic neuritis (normal brain MRI and negative for neuromyelitis optica IgG antibodies), 1 developed chronic recurrent inflammatory optic neuritis (normal brain and spine MRI and negative for neuromyelitis optica IgG antibodies), and 1 had acute disseminated encephalomyelitis (also with encephalopathy and transverse myelitis, abnormal brain MRI at onset, negative for neuromyelitis optica IgG antibodies, normal brain MRI, and no relapse at 3.5-year follow-up). Three eyes of patients who presented with acute vision loss and an abnormal brain MRI were months later determined to have had nonarteritic ischemic optic
neuropathy. Eyes with incomplete recovery from nonarteritic ischemic optic neuropathy did not differ in mean DTI parameters at onset from those with acute optic neuritis (fractional anisotropy $P = .77$, mean diffusivity $P = .84$, AD $P = .97$, and radial diffusivity $P = .81$); analyses were performed with and without inclusion of subjects with nonarteritic ischemic optic neuropathy.

**LOW BASELINE AD AS A PREDICTOR OF INCOMPLETE VISUAL RECOVERY AT 6 MONTHS**

Baseline AD differentiated subjects with complete clinical recovery by 6 months (1.75 µm²/ms [95% CI, 1.67-1.83 µm²/ms]) from those with incomplete recovery by 6 months (1.50 µm²/ms [95% CI, 1.36-1.64 µm²/ms]). Odds of complete 6-month recovery decreased by 53% (95% CI, 27%-70%) for every 0.1-unit decrease in AD at baseline. When both baseline AD and visual acuity were included as covariates in a predictive model of 6-month recovery, AD continued to provide an independent prognostic value ($P = .03$). Additional covariates in the model for predicting outcome were not significant, including age ($P = .58$), sex ($P = .68$), and use of intravenous glucocorticoids ($P = .39$). After excluding the 3 subjects who were later diagnosed with nonarteritic ischemic optic neuropathy, we found that a low AD continued to predict 6-month incomplete recovery (odds ratio, 0.47 [95% CI, 0.18-0.65]; $P = .03$). Thus, AD was a predictor of outcome in subjects with inflammatory and demyelinating optic neuritis.

Affected eyes with incomplete recovery demonstrated a lower mean AD (1.50 µm²/ms [95% CI, 1.36-1.64 µm²/ms]) than did unaffected fellow eyes (1.79 µm²/ms [95% CI, 1.67-1.91 µm²/ms]). Affected eyes with complete recovery (1.75 µm²/ms [95% CI, 1.67-1.83 µm²/ms]) were not different from the unaffected fellow eyes. Both incomplete and complete recovery AD values were within 2 SDs of the mean (SD) AD value for healthy controls, 1.66 (0.18) µm²/ms (interscan SD, 0.12; intrascan SD, 0.13).[^16]

**CORRELATION BETWEEN LOW BASELINE AD AND WORSE CLINICAL OUTCOME MEASURES AT 6 MONTHS**

Baseline AD correlated with the 6-month visual acuity ($r=0.40, P = .03$), 5% contrast sensitivity ($r=-0.45, P = .01$), and Pelli-Robson contrast sensitivity ($r=0.41, P = .02$) (Table 2). When evaluating only those cases of optic neuritis with moderate to severe onset (visual acuity, ≤0.5), we found that AD continued to correlate with the 6-month 5% contrast sensitivity ($r=0.43, P = .05$) and Pelli-Robson contrast sensitivity ($r=0.48, P = .03$). In addition, lower values of baseline AD correlated with lower VEP amplitudes ($r=0.53, P < .01$), thinner RNFLs ($r=0.57, P = .02$), and the prolongation of VEP latencies ($r=-0.38, P = .04$) at 6 months. Mean diffusivity demonstrated more variable correlations with 6-month clinical outcomes (Table 2).

### Table 1. Baseline Characteristics of 25 Subjects Who Presented Within 31 Days After Acute Visual Symptoms Consistent With Optic Neuritis[^4]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases, No. (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>29 (19-59)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female 23 Male 8</td>
</tr>
<tr>
<td>Time to initial visit, d</td>
<td>12.5 (1.0-31.0)</td>
</tr>
<tr>
<td>Use of IV methylprednisolone</td>
<td>No 13 Yes 18</td>
</tr>
<tr>
<td>sodium succinate</td>
<td></td>
</tr>
<tr>
<td>Diagnoses per nerve</td>
<td>Clinically isolated syndrome 19 Isolated optic neuritis 7 Nonarteritic ischemic optic neuropathy 3 Chronic recurrent inflammatory optic neuropathy 1 Acute disseminated encephalomyelitis 1</td>
</tr>
<tr>
<td>Visual acuityb</td>
<td>0.2 (0.0-1.0)</td>
</tr>
<tr>
<td>5% contrast sensitivity, logMAR</td>
<td>1.0 (0.1-1.0)</td>
</tr>
<tr>
<td>Pelli-Robson contrast sensitivity, logMAR</td>
<td>0.85 (0.09-1.75)</td>
</tr>
<tr>
<td>RNFL thickness, c</td>
<td>79.61 (51-136.90)</td>
</tr>
<tr>
<td>VEP N75:N100 amplitude, µV</td>
<td>6.39 (1.50-10.70)</td>
</tr>
<tr>
<td>VEP P100 latency, ms</td>
<td>150 (117-170)</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; VEP, visual evoked potential.

[^4]: Subjects with good visual acuity required objective evidence of optic neuritis (ie, abnormal contrast sensitivity, pain with lateral eye movement, afferent pupillary defect, VEP abnormality, and OCT-determined papillitis) by additional testing.

[^5]: Based on the resolution adopted by the International Council of Ophthalmology.[^19]

[^6]: Determined by use of OCT.

**POOR VISUAL ACUITY AT ONSET AS A PREDICTOR OF WORSE RECOVERY**

Visual acuity at onset was not predictive of visual acuity at 6 months ($r=0.31, P = .04$). In the aggregate, baseline visual acuity was a predictor of 6-month Pelli-Robson contrast sensitivity ($r=0.43, P = .02$), although for the 21 subjects with moderate to severe loss of vision at presentation (visual acuity, ≤0.5), visual acuity was not a predictor of Pelli-Robson contrast sensitivity ($r=0.03, P = .91$). For the entire group, visual acuity at baseline was not a predictor of 5% contrast sensitivity at 6 months ($r=-0.16, P = .39$).

**CORRELATION BETWEEN LOW AD AND WORSE BASELINE CLINICAL MEASURES**

Axial diffusivity at baseline had moderate correlations with baseline visual acuity ($r=0.49, P < .01$), 5% contrast sensitivity ($r=-0.40, P = .02$), and Pelli-Robson contrast sensitivity ($r=0.50, P < .01$) (Table 2). Mean diffusivity had similar baseline correlations (Table 2).

**TIME COURSE FOR LOW AD**

Low AD was confined to the first month. Axial diffusivity for the group was 1.58 µm²/ms (95% CI, 1.50-1.66 µm²/ms) over the first month, increasing at 3 months to...
The table shows correlations between baseline and 6-month outcome measures in diffusion tensor imaging (DTI) parameters and clinical measures. The table includes values for AD, FA, RD, and MD at baseline and 6 months, as well as correlations with clinical measures such as VA, RNFL thickness, and VEP latency. The table also highlights significance at P < .05.

Figure 1 illustrates the time course of changes in the parameters used in DTI imaging for the optic nerves of subjects from onset of optic neuritis to 12 months. The parameters are mean diffusivity, fractional anisotropy, and radial diffusivity. The figure shows that mean diffusivity and fractional anisotropy demonstrate a trend toward further alteration over the latter 9-month interval.

After dividing subjects by recovery status, it was found that early recovery was associated with lower mean AD (1.51 µm²/ms [95% CI, 1.36-1.66 µm²/ms]) compared with later baseline imaging, and that 6 months later (1.94 µm²/ms [95% CI, 1.80-2.08 µm²/ms]) for the incomplete group vs 1.90 µm²/ms [95% CI, 1.80-1.99 µm²/ms] vs 1.95 µm²/ms [95% CI, 1.80-2.10 µm²/ms]).

Further statistical modeling revealed that time to presentation was not a significant predictor of recovery (P = .57), whereas AD continued to predict recovery status (P < .001). After subdividing the time of baseline imaging into early (0-15 days) vs later (16-31 days), we found that the early group displayed a mean AD of 1.51 µm²/ms (95% CI, 1.36-1.66 µm²/ms) when recovery was incomplete compared with 1.70 µm²/ms (95% CI, 1.60-1.80 µm²/ms) when recovery was complete. For those in the incomplete recovery group with later baseline imaging, the mean AD was 1.51 µm²/ms (95% CI, 1.37-1.66 µm²/ms), and for those in the complete group with later baseline imaging, the mean AD was 1.69 µm²/ms (95% CI, 1.48-1.90 µm²/ms). These results qualitatively suggest that predictive imaging can be achieved within 3 to 4 weeks of clinical onset.

RADIAL DIFFUSIVITY OVER THE NEXT 12 MONTHS

Radial diffusivity for the group was normal during the first month (divided into 0.91 µm²/ms [95% CI, 0.84-0.98 µm²/ms] at 2 weeks and 0.96 µm²/ms [95% CI, 0.88-1.03 µm²/ms] at 4 weeks) and progressively increased over the ensuing year (Figure 1). The greatest rate of change was observed between months 1 and 2 (mean [SE], 0.085 [0.053] µm²/ms per month), followed by months 2 and 3 (mean [SE], 0.071 [0.054] µm²/ms per month). By 3 months, overall radial diffusivity was clearly elevated (1.11 µm²/ms [95% CI, 1.03-1.19 µm²/ms]) compared with baseline radial diffusivity, and it continued to remain elevated at 6 months (1.22 µm²/ms [95% CI, 1.13-1.30 µm²/ms]) and 12 months (1.30 µm²/ms [95% CI, 1.21-1.40 µm²/ms]). Mean diffusivity and fractional anisotropy, simi-
lar to radial diffusivity, became clearly abnormal by month 3, and they continued to be altered through month 12 (Figure 1).

At 12 months, radial diffusivity in the incomplete recovery group (1.45 µm²/ms [95% CI, 1.31-1.59 µm²/ms]) could be differentiated from radial diffusivity in the recovered group (1.19 µm²/ms [95% CI, 1.10-1.28 µm²/ms]) (Figure 2). Also, by 12 months, fractional anisotropy in the incomplete recovery group (0.25 [0.20-0.29]) could be differentiated from fractional anisotropy in the complete recovery group (0.33 [0.30-0.36]).

**COMMENTS**

Our study establishes that low AD during the initial episode of optic neuritis is a predictor of incomplete visual recovery. Low AD at presentation was consistently associated with worse performance among 6-month clinical measures of vision, which included visual acuity, 5% contrast sensitivity, and Pelli-Robson contrast sensitivity. After accounting for baseline visual acuity and demographics, we found that AD provided a significant contribution to risk stratification. Furthermore, initial AD was associated with a smaller VEP amplitude and a thinner RNFL at 6 months, in addition to a prolonged VEP latency. Because it is not possible to obtain histopathologic data from acutely affected human optic nerves, the results from these ancillary tests, in the context of prior animal imaging and pathologic data, lend support to a relationship between low AD, more severe tissue damage, and axon injury in acute optic neuritis. In contrast, radial diffusivity and mean diffusivity were not significantly altered at baseline and did not consistently predict clinical outcomes. Data on radial diffusivity and fractional anisotropy did help us to differentiate outcomes in remote optic neuritis, 12 months later.

The optic nerve provides an opportunity to test DTI on a white matter tract with clear clinical end points. Optic neuritis is pertinent to MS, has a discreet clinical onset, and can result in significant disability. Studying the optic nerve with DTI is 1 step in a methodological approach to validate an imaging technique through animal models and human autopsy material with histopathologic correlation, and within different regions of the central nervous system, on a longitudinal and cross-sectional basis. Studying the optic nerve is part of a comprehensive approach to validate DTI for clinical trials and eventually clinical practice.
A decreased mean diffusivity has previously been appreciated in acute MS lesions, but the cause remains unclear. Decreased diffusion is typically seen in acute stroke, when ischemia is believed to result in membrane ion channel pump failure, intracellular sodium accumulation, and cytotoxic edema. Acute demyelinating lesions are not typically associated with cytotoxic edema but with vasogenic edema and increased mean diffusivity. Thus, the low AD in our study is unlikely to be due to acute optic nerve swelling from vasogenic edema. In our study, the decrease in AD was no longer evident past 1 month from clinical onset. This may reflect that, as macrophages and other inflammatory cells infiltrate the tissue and clear myelin debris, the axons comprise a smaller proportion of the tissue, lessening their contribution to diffusivity. Although normal at baseline, radial diffusivity increased steeply over the next 1 to 3 months, perhaps indicating continued demyelination with myelin debris clearance.

Within acute MS lesions, early metabolic derangements may result in failure of ion channels and transport mechanisms in axons. Organelle and protein accumulation may lead to increased intra-axonal viscosity and axonal swelling, contributing to a decrease in AD. Compromised axonal transport in acute axonal injury has been previously demonstrated by the accumulation of the β-amyloid precursor protein. Some reports of MS tissue qualitatively describe swollen or beaded axons on the longitudinal or the oblique section, and such structural alterations may contribute to alterations of AD in the acute setting.

Other longitudinal studies have investigated quantitative imaging in acute optic neuritis. In contrast to DTI, the magnetization transfer ratio of the optic nerve was normal during acute optic neuritis and progressively decreased over the next 8 months. Recovery of the magnetization transfer ratio during the last third of the first year correlated with visual recovery, emphasizing the role of complementary quantitative imaging. Another study demonstrated increased optic nerve volume at onset through 3 months, although neither optic nerve swelling nor atrophy was associated with visual outcome.

A prior study of DTI within acute enhancing brain lesions found no relationship between low AD and risk for chronic T1 hypointensity (a surrogate for axonal loss). In our study, DTI was focused on a directional and compact white matter tract. Although the brain does contain well-organized white matter tracts, lesions also occur within regions of low anisotropy and crossing fibers. Thus, studying AD changes in the brain may require a method capable of resolving multiple tensors to elucidate crossing fibers and to separate the axonal and demyelinating components from edema, cellular infiltration, and widening interstitial spaces. In contrast to radial diffusivity and mean diffusivity in the optic nerve, radial diffusivity and mean diffusivity in the brain may hold more potential within both acute and chronic lesions. Understanding the dynamics of DTI changes in response to injury within different regions of the central nervous system may assist in further assessments of prognosis and treatment.

Diffusion tensor imaging of the optic nerve could be used in multicenter clinical studies with special provisions. It might also be used in the future to stratify risk for incomplete recovery and to identify subjects who may benefit from an early therapeutic intervention. Obtaining high-resolution 1.3-mm isotropic voxels permits the inclusion of the optic nerve center, and optimal signal is achieved by a surface coil, 3-T MRI scanner, and multiple averages. Care in preparing and positioning the patient, along with an imaging session dedicated only to optic nerve imaging, will ensure minimal movement during the 40-minute sequence.

Diffusion tensor imaging provides a noninvasive means to quantify tissue changes on a longitudinal basis in the human central nervous system, a region in which serial histological evaluations are not feasible. Multiple sclerosis lesions display varying combinations of axonal injury, demyelination, and inflammation with diverse inflammatory cell populations, all of which change over time. In addition, severe demyelination may lead to chronic loss of function indistinguishable from axonal injury; all disability in MS may not be attributable to a single pathologic process. Diffusion tensor imaging may provide a more specific window into the pathology of MS, which is recognized to be heterogeneous, complex, and dynamic. Future studies of directional diffusivities in the brain and spinal cord are planned to further elucidate the relationship between tissue integrity, MS lesion evolution, and clinical outcomes.

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Author Contributions: Dr Naismith had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Naismith and Xu contributed equally as co-first authors. Drs Song and Cross contributed equally as co–senior authors. Study concept and design: Naismith, Song, and Cross. Acquisition of data: Naismith, Xu, Tutlam, and Lancia. Analysis and interpretation of data: Naismith, Xu, Trinkaus, and Cross. Drafting of the manuscript: Naismith. Critical revision of the manuscript for important intellectual content: Xu, Tutlam, Lancia, Trinkaus, Song, and Cross. Statistical analysis: Trinkaus. Obtained funding: Naismith and Song. Administrative, technical, and material support: Naismith, Xu, Tutlam, Lancia, Song, and Cross. Study supervision: Cross.

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from the publication of *Handbook of Multiple Sclerosis, 4th ed* (Taylor & Francis Group, 2006); serves on speakers' bureaus for Bayer Schering Pharma, Biogen Idec, and Teva Neurosciences; has received speaker honoraria from Amgen and Pfizer Inc; and receives research support from sanofi-aventis, Acorda Therapeutics, Genentech Inc, Biogen Idec, the NIH and the National Institute of Neurological Disorders and Stroke (grants PO1 NS059560-01 [principal investigator], U01 NS45719-01A1 [coinvestigator], R01 NS47592 [coinvestigator], and R01 NS 051591 [principal investigator]), Washington University Institute of Clinical and Translational Sciences, the National Multiple Sclerosis Society, the Consortium of Multiple Sclerosis Centers, and the Barnes-Jewish Hospital Foundation.

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**REFERENCES**