Factors associated with recovery from acute optic neuritis in patients with multiple sclerosis

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ABSTRACT

Objective: To identify clinical and demographic features associated with the severity and recovery from acute optic neuritis (AON) episodes in patients with multiple sclerosis (MS).

Methods: Adult (n = 253) and pediatric (n = 38) patients whose first symptom was AON were identified from our MS database. Severity measured by loss of visual acuity (mild attack ≤20/40, moderate attack 20/50–20/190, and severe attack ≥20/200) and recovery in visual acuity at 1 year after the attack (complete recovery ≤20/20, fair recovery 20/40, and poor recovery ≥20/50) were recorded. Demographic and clinical features associated with attack severity and recovery were identified using proportional odds logistic regression. For another group of patients, blood samples were available within 6 months of an AON attack. In this group, the impact of vitamin D level on the severity/recovery was also assessed.

Results: Men (adjusted odds ratio [OR] = 2.28, $p = 0.03$) and subjects with severe attacks (adjusted OR = 5.24, $p < 0.001$) had worse recovery. AON severity was similar between the pediatric and adult subjects, but recovery was significantly better in pediatric subjects in the unadjusted analysis ($p = 0.041$) and the analysis adjusted for sex ($p = 0.029$). Season-adjusted vitamin D level was significantly associated with attack severity (OR for 10-U increase in vitamin D level = 0.47; 95% confidence interval: 0.32, 0.68; $p < 0.001$). Vitamin D level was not associated with recovery from the attack ($p = 0.98$) in univariate analysis or after accounting for attack severity ($p = 0.10$).

Conclusion: Vitamin D levels affect AON severity, whereas younger age, attack severity, and male sex affect AON recovery. Underlying mechanisms and potential therapeutic targets may identify new measures to mitigate disability accrual in MS. *Neurology*® 2014;82:2173–2179

GLOSSARY

AOMS = adult-onset multiple sclerosis; **AON** = acute optic neuritis; **CIS** = clinically isolated syndrome; **CLIMB** = Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women's Hospital; **MS** = multiple sclerosis; **NMO** = neuromyelitis optica; **OR** = odds ratio; **PMS** = pediatric multiple sclerosis.

Acute optic neuritis (AON) is an inflammatory disorder of the optic nerve and the initial presenting symptom of multiple sclerosis (MS) in approximately 15% to 20% of patients.[1,2] There is wide variability in the severity and recovery from AON among patients with MS, and clinical predictors of AON severity or recovery are not well understood. Previous work has demonstrated that severity and recovery from the initial relapse are associated with severity and recovery for subsequent relapses, but factors specifically affecting AON attacks have not been sufficiently studied.[3]

One potentially important predictor of disability accrual and disease course in MS is age at disease onset. Younger patients may have improved recovery from relapses in general[4,5] and slower disease progression,[6] despite a more inflammatory initial course of disease.[5,7] Despite the frequency at which AON occurs in MS, there is limited information about the impact of age on the severity and recovery from AON. Beyond age at onset, several other demographic factors, including sex and disease duration, are associated with aspects of the disease course in MS.

In addition to demographic features, vitamin D level has been shown to be a potential predictor of disease activity.[8,9] In particular, low vitamin D levels are associated with an increased relapse rate

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in patients with pediatric MS (PMS)[8] and an increased number of enhancing lesions in patients with adult-onset MS (AOMS).[9] Despite the association with an increased risk of relapse, little is known about the association between vitamin D level and severity or recovery from attacks.

The goals of this study were (1) to identify clinical and demographic predictors of AON severity and recovery in an AOMS sample, (2) to compare patients with PMS to patients with AOMS for AON severity/recovery, and (3) to assess the association of vitamin D level immediately after an attack on AON severity/recovery.

METHODS

Subjects. Three groups of subjects participated in this study. The first group consisted of 253 subjects with AON as their initial presenting symptom, selected from the Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women's Hospital (CLIMB) Study at the Partners MS Center.[10] The CLIMB is an ongoing prospective observational cohort study initiated in year 2000, in which attacks, visits, treatment data, and other features are prospectively entered into a relational database. To ensure that subjects had sufficient information to assess severity and recovery from the initial AON attack, subjects were required to have first AON after 2000. Additional inclusion criteria included age older than 18 years at the time of first symptom, patients who met McDonald 2010 criteria[11] for relapsing-remitting MS, and clinically isolated syndrome (CIS) with T2 lesions on brain MRI. Subjects with neuromyelitis optica (NMO), acute demyelinating encephalomyelitis, and progressive-onset MS were excluded from the study. The second group included 38 patients with PMS or CIS meeting IPMSSG (International Pediatrics Multiple Sclerosis Study Group) criteria seen at the Partners Pediatric MS Center, Massachusetts General Hospital, who presented with AON as their initial attack. The third group consisted of subjects from the CLIMB Study who had a serum sample drawn within 6 months after any AON attack (n = 101). For these subjects, AON was not required to be the initial presenting symptom. All clinical and relapse data from all patients were retrieved from our Oracle relational database and validated by our staff (M.T.M., L.A.B.) using each patient's longitudinal medical record. In addition, treatment and steroid history was validated for each patient. The demographic features of each group are provided in table 1.

Standard protocol approvals, registrations, and patient consents. Institutional Review Board approval was granted by the Partners Human Research Committee.

Severity and recovery definitions. An AON attack was defined as a new neurologic symptom involving at least one eye associated with pain on eye movements, double vision, and decrease in visual acuity lasting more than 24 hours without concurrent fever or illness. The presence of the bilateral involvement of the optic nerve was recorded. The severity of each attack was gathered from clinician notes, and attack severity was classified into 3 categories according to the decrease in the visual acuity measured or reported to clinicians during the time of the attack based on definitions from previous publications.[3,12–14] A mild attack was defined as a decrease in visual acuity to at most 20/40 in the affected eye, a moderate attack was defined as a decrease in visual acuity to between 20/50 and 20/190, and a severe attack was defined as a decrease in visual acuity equal to or worse than 20/200.

Recovery from AON attacks was determined at the follow-up visit, which was 1 year from the time of attack (±90 days). Recovery from the attack was defined using 3 categories depending on the visual acuity at the time of the follow-up visit. Complete recovery was defined as visual acuity with correction of 20/20. Fair recovery was defined as visual acuity in the range of 20/40 or better, while poor recovery was defined as visual acuity of 20/50 or worse.[12,13]

Vitamin D levels. Serum samples collected between 0 and 6 months after the attack of optic neuritis were analyzed at the Harvard NeuroDiscovery Center Clinical laboratory using the chemiluminescent microparticle immunoassay, for the quantitative determination of 25-hydroxyvitamin D (25-OH vitamin D) in human serum (Abbott, Abbott Park, IL). The 25-OH vitamin D measurements were then adjusted for season using the previously published formula (see appendix e-1 on the *Neurology*® Web site at Neurology.org).

Statistics. The severity and recovery data from the first AON in patients with AOMS (group 1) were tabulated. The impact of demographic features (age, sex, race, and ethnicity) on severity and recovery was assessed using a proportional odds logistic regression model. The effect of steroid infusions at the time of the attack and disease-modifying therapy in the year after the

Table 1 Demographic characteristics of patients with AOMS and PMS with AON attacks

	AOMS	PMS	Vitamin D subset
No.	253	38	101
Age at AON attack, mean (SD)	34.7 (9.6)	14.7 (3.0)	32.2 (11.3)
Sex, % female	79.4	63.2	80.2
Ethnicity, % Hispanic[a]	2.77	14.29	11.88
Race, % white[a]	90.68	91.18	87.12
Disease category: MS, CIS	208, 45	24, 14	89, 12
Affected eye: left, right, both	122, 117, 14	20, 11, 7	47, 42, 12
Steroids at time of attack, % treated	43.9	60.5	68.3
Treatment at recovery visit, % treated at 1-year follow-up visit	63.2	42.1	80.19

Abbreviations: AOMS = adult-onset multiple sclerosis; AON = acute optic neuritis; CIS = clinically isolated syndrome; MS = multiple sclerosis; PMS = pediatric multiple sclerosis.
[a] In 21 subjects, ethnicity information was missing, and in 21 subjects, race information was missing.

Table 2 Assessment of first AON attack severity and recovery in the AOMS and PMS groups

	AOMS	PMS	Unadjusted *p* value[a]	Adjusted *p* value[b]
Attack				
Mild (1)	28 (11.1)	5 (13.16)	0.75	0.66
Moderate (2)	103 (40.7)	13 (34.21)		
Severe (3)	122 (48.2)	20 (52.63)		
Recovery				
Complete (1)	202 (79.8)	36 (94.74)	0.041[c]	0.029[c]
Fair (2)	23 (9.1)	1 (2.63)		
Poor (3)	28 (11.1)	1 (2.63)		

Abbreviations: AOMS = adult-onset multiple sclerosis; AON = acute optic neuritis; PMS = pediatric multiple sclerosis.
Data are n (%).
[a] The *p* value from proportional odds logistic regression model comparing PMS with AOMS.
[b] Adjusted *p* value from proportional odds model adjusting for sex.
[c] Significant values.

attack on the level of recovery was also assessed. To assess whether the severity or recovery of the first AON attack was associated with the severity or recovery of the second AON attack, the severity or recovery of the first attack was included as a predictor in a proportional odds model for the severity or recovery of the second attack. To further investigate the impact of age on severity and recovery from AON, the levels of severity and recovery were compared in the AOMS and PMS groups using a proportional odds model. Furthermore, the association between severity and recovery from the first attack and severity and recovery from the second attack was assessed in the patients with PMS and compared to the patients with AOMS using appropriate interaction terms. The AON relapse rate was also calculated in both patient groups, and the groups were compared using Poisson regression with an overdispersion parameter and offset for length of follow-up. For the calculation of the relapse rate, the first relapse was removed from the analysis. To assess the effect of vitamin D level on the severity and recovery of the attack, the seasonally adjusted vitamin D level was included as a predictor in the same proportional odds models as above.

Table 3 Predictors of AON attack severity and recovery in patients with AOMS

Feature	OR	*p* Value
Severity		
Age at onset[a]	1.02	0.86
Male vs female	1.02	0.96
White vs nonwhite	0.65	0.31
Hispanic vs non-Hispanic	1.05	0.94
Steroids	4.94	<0.0001
Bilateral vs unilateral	0.41	0.072
Recovery		
Age at onset[a]	1.09	0.61
Male vs female	2.01	0.049
White vs nonwhite	1.12	0.85
Hispanic vs non-Hispanic	0.78	0.82
Steroids vs no steroids	2.09	0.020
Treatment vs no treatment	0.69	0.24
Severity	5.29	<0.001
Bilateral vs unilateral	1.44	0.54

Abbreviations: AOMS = adult-onset multiple sclerosis; AON = acute optic neuritis; OR = odds ratio.
Reported OR is from a proportional odds logistic regression model. An OR >1 indicates that the first group is associated with increased odds of worse severity or recovery.
[a] OR for age is for a 10-year increase in age at onset.

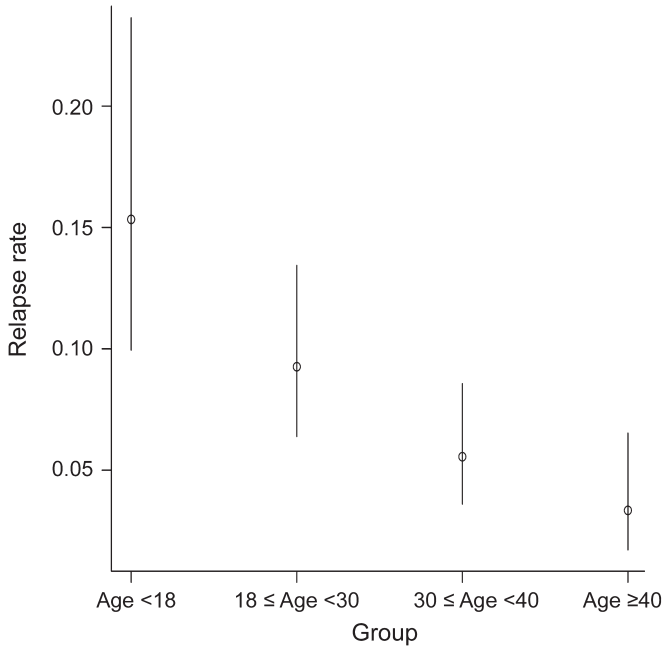
RESULTS

Severity and recovery from AON. The severity and recovery data from the first attack of AON in patients with AOMS are provided in table 2. Severe AON attacks were the most common (48.2%), and mild attacks were rarely observed (11.1%). None of the demographic features were significantly associated with severity of the first attack (table 3). The majority of patients had complete recovery from the first attack (79.8%), and a smaller percentage of patients had either a fair or poor recovery (20.2%). Male sex, increased severity of the attack, and steroids were each associated with worse AON recovery in univariate models (table 3). When sex, severity of the attack, and steroids were included in the same model, sex and severity remained significantly associated with recovery, demonstrating that each of these factors is independently related to recovery. In particular, men had worse recovery (adjusted odds ratio [OR] = 2.27, $p = 0.03$), and subjects with more severe attacks had worse recovery (adjusted OR = 5.31, $p < 0.001$). In the multivariable model, steroid use had no association with recovery ($p = 0.81$), demonstrating that the negative association with steroids in the original model is attributable to more severe attacks being treated with steroids rather than a true negative effect of steroids. Disease category of MS or CIS had no effect on severity or recovery.

To assess whether severity/recovery from the first attack was associated with severity/recovery from the second attack, subjects with at least 2 attacks were identified (n = 57). The severity of the first attack was not significantly associated with the severity of the second attack ($p = 0.29$). Conversely, the recovery from the first attack was significantly associated with the recovery from the second attack ($p = 0.001$).

Comparison of PMS and AOMS. The severity of AON attacks at first symptoms in patients with PMS was not significantly different than the severity in the patients with AOMS in either the unadjusted analysis or after adjusting for sex (table 2). However, recovery from the initial presentation of AON in patients with AOMS was significantly worse than the recovery in patients with PMS in both the unadjusted analysis and after adjusting for sex (table 2). Of the 2 patients with PMS who had poor recovery at their 1-year visit, one had full recovery after the 1-year visit while the other still had a residual visual deficit of 20/200 in the affected eye. Predictors of AON severity are listed in table 3.

Figure 1 Acute optic neuritis attacks according to the different decades of disease onset



Estimated relapse rate and associated 95% confidence interval based on the Poisson regression model with an overdispersion parameter and offset for length of follow-up are presented.

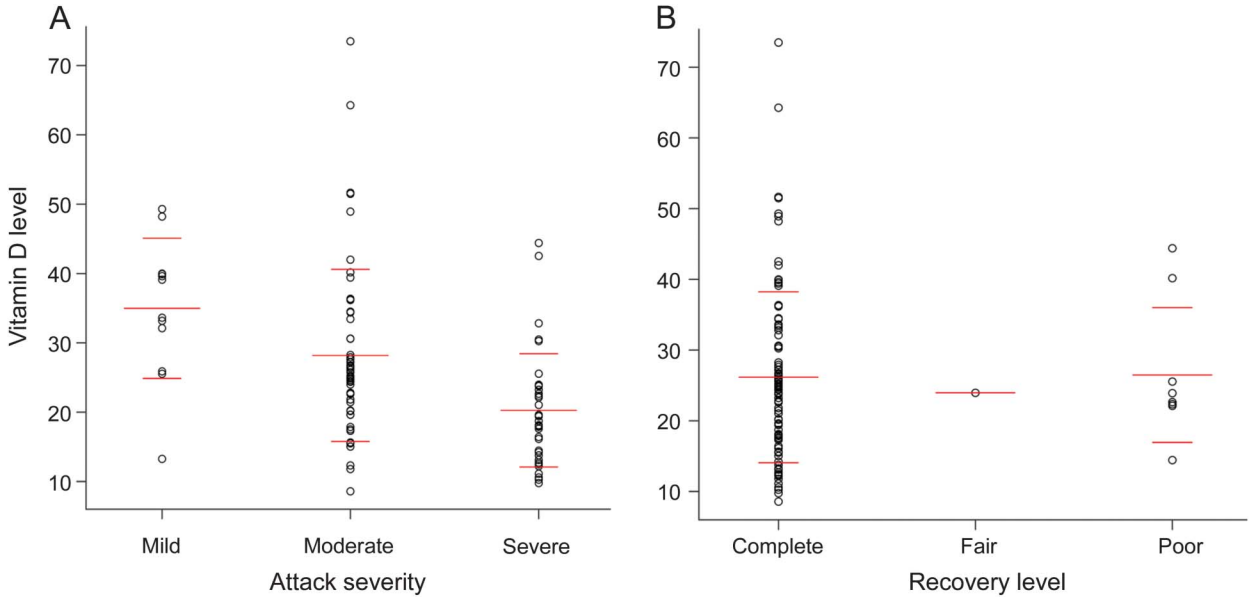
When the association between the first and second relapse was assessed, the severity of the second attack was significantly associated with severity of the first attack in patients with PMS ($p = 0.016$). In addition, the impact of the first attack on the second attack was significantly stronger in PMS compared with AOMS ($p = 0.025$). The relationship between recovery from the first and second attack was not significantly different comparing the AOMS with the PMS group ($p = 0.44$).

The AON relapse rate in patients with PMS was estimated as 0.15 relapses per patient-year compared with the AON relapse rate in patients with AOMS of 0.06 relapses per patient-year, and the difference between the groups was statistically significant (rate ratio = 2.50; 95% confidence interval: 1.48, 4.20; $p = 0.0007$). In addition, the AON relapse rate consistently declined with increasing age at the first symptoms (figure 1).

Impact of vitamin D on AON. A group of patients had a blood sample drawn within 6 months of an AON attack. For 23 patients, the attack associated with the blood sample was the patient's first attack. For an additional 35 patients, the attack was not the first attack of the disease, but it was the first episode of AON. For the remaining 43 patients, the attack was not the first AON attack in the disease course. The demographic characteristics of the patients in this group were similar to those of the AOMS group with a sample at the first attack.

In this group of patients, 12 of 101 patients (11.9%) had a mild attack, 53 of 101 (52.5%) had a moderate attack, and 36 of 101 (35.6%) had a severe attack. Ninety-one of 101 (90.1%) had a complete recovery, 1 of 101 (1.0%) had fair recovery, and 9 of 101 (8.9%) had poor recovery. Because the number of previous AON attacks was not significantly associated with severity ($p = 0.77$) or recovery ($p = 0.65$), all attacks were analyzed together. The season-adjusted vitamin D level was significantly associated with severity of the attack (OR for 10-U increase in vitamin D level = 0.47; 95%

Figure 2 Vitamin D levels according to attack severity and recovery in patients with acute optic neuritis



For each graph, the seasonally adjusted 25-OH vitamin D levels (ng/mL) are shown stratified by attack severity (A) and recovery level (B). The middle red line for each level shows the mean. The top (bottom) red line represents 1 SD above (below) the mean.

confidence interval: 0.32, 0.68; $p < 0.001$) (figure 2). The level of vitamin D was not associated with recovery from the attack ($p = 0.98$) in a univariate analysis or after accounting for attack severity ($p = 0.10$) (figure 2).

DISCUSSION Despite the large body of information about AON from observational studies[15,16] and clinical trials,[17] limited information exists regarding predictors of severity and recovery from AON attacks. Our results demonstrate that no clinical or demographic predictors are significantly associated with severity, but male sex and attack severity are independently associated with recovery. Furthermore, patients with PMS have significantly better recovery than patients with AOMS. In addition, we found that vitamin D level measured after the attack is associated with worse attack severity.

One of the main clinical goals in treating patients with MS who have AON is to ensure that the recovery is quick and complete. Therefore, identifying patient characteristics and other modifiable risk factors associated with recovery can allow us to better understand how patients recover. As demonstrated in our study and previous studies,[4,18] the strongest predictor of recovery is attack severity. Given this relationship, predictors of both attack severity and attack recovery can provide valuable information about the clinical course of patients with AON.

Regarding predictors of attack severity, the results demonstrated that none of the demographic features studied were significantly associated with severity. In contrast, vitamin D level was significantly associated with disease severity, and subjects with lower seasonally adjusted vitamin D levels were more likely to have severe attacks. Vitamin D level is a known modifiable risk factor for the development of MS,[19] and more recent studies have demonstrated a relationship between vitamin D level and attack frequency[20] and response to treatment.[8,9] No previous study has specifically investigated the importance of vitamin D in the severity of AON, and our results support the hypothesis that low vitamin D levels are related to worse MS disease course. A potential explanation for our result is that subjects with more severe attacks change their behavior, which then leads to lower vitamin D levels. Previous research has demonstrated that vitamin D levels have a lag such that changes in behavior should not affect vitamin D levels for at least 6 to 8 weeks.[21,22] When we reanalyzed the data using only patients with samples taken within 2 months of the attack, vitamin D level still had a significant association with attack severity (data not shown).

Severity of the attack and male sex were each independently associated with worse attack recovery. The difference between males and females adds to a growing body of literature showing sex differences in the MS disease course.[23] Many early longitudinal studies in MS have shown that males have worse prognosis than females in part because of the increased likelihood of a primary progressive disease course.[24–27] More recent evidence has focused on the potential role of testosterone on the disease course of MS,[28] but few studies have specifically investigated the role of sex in recovery from AON. Some studies conducted in the experimental autoimmune encephalomyelitis animal models of MS have shown the protective role of testosterone.[29,30] Therefore, one possible explanation of poor recovery in males may be attributable to the decrease in androgen levels with increasing age. In our study, the onset of disease in males was slightly later than in the females, but this difference was not statistically significant. Future studies should investigate whether androgen levels in males are associated with attack severity to assess one potential explanation for the sex difference.[23]

Although age was not significantly associated with recovery in only the patients with AOMS, the patients with PMS were significantly more likely to have a complete recovery, which may indicate better repair potential in PMS compared with AOMS. In addition, the AON relapse rate in the PMS group was significantly higher than in the AOMS group, reinforcing our results from previous studies suggesting that patients with PMS are more likely to experience an active disease course compared with patients who have AOMS.[7,18,25] The combination of increased relapse rate but improved recovery might explain the reason that patients with PMS have more inflammatory disease but slower disability accumulation.[31]

Previous studies have demonstrated that severity of and recovery from attacks are associated within a subject, and this result may demonstrate that patients follow a similar path throughout the disease course.[3] To validate this finding, the association among AON attacks within a subject was assessed. No significant association was observed between the severities of the AON attacks in the patients with AOMS, but a significant association was observed between the recoveries of the attacks. Of note, within the PMS group, the severity of the first attack was associated with severity of the second attack and the impact of the first attack was much stronger in this group, suggesting that the disease course within patients with PMS is more homogeneous than that in patients with AOMS.[7] Disease category of MS or CIS had no effect on severity or recovery in either the AOMS or PMS group. As in the Optic Neuritis Treatment Trial, we did not find an effect of use of IV steroids on recovery from optic neuritis in the longer term.[13] Our study differs from the Optic Neuritis Treatment Trial in that we focused on patients with MS, excluding all patients who were diagnosed with NMO or NMO spectrum disease.

Our study has some limitations that require additional discussion. Those who were validating the data for the AON attacks were not completely blinded to

the study, but rigid classification of the AON attack severity and recovery was used, which makes misclassification bias highly unlikely. Visual acuity at baseline was carefully documented from the clinician's notes, and patients with any other complicating ophthalmologic conditions were excluded from this study. While the cohort for the AOMS was quite large, the PMS group was relatively small, in part because only CIS and relapsing-remitting MS variants were included, whereas others, including NMO, were excluded.

Our study showed that patients who present with severe AON are more likely to have a poor recovery and may have a tendency to continue on a similar trajectory. Vitamin D may have an important role in determining AON attack severity, but larger samples are required to validate this finding. Better recovery in younger patients in the comparison between AOMS and PMS groups suggests age-related recovery mechanisms. This may provide new insights into the prevention of disability accrual in patients with MS. Male sex and hormonal mechanisms may also contribute to AON recovery and require further exploration.

AUTHOR CONTRIBUTIONS

Dr. Malik contributed to study concept and design, acquisition of data, and analysis and interpretation, and prepared the first draft of the manuscript. Dr. Healy contributed to study concept and design, analysis and interpretation, and critical revision of the manuscript for important intellectual content. Dr. Benson and Dr. Kivisakk contributed to the acquisition of data and critical revision of the manuscript for important intellectual content. Mr. Musallam contributed to data analysis and interpretation and critical revision of the manuscript for important intellectual content. Dr. Weiner contributed to critical revision of the manuscript for important intellectual content and study supervision. Dr. Chitnis contributed to study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, and study supervision.

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This Week's *Neurology*® Podcast

Factors associated with recovery from acute optic neuritis in patients with multiple sclerosis **(See p. 2173)**

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the June 17, 2014, issue of *Neurology*. In the second segment, Dr. Mark Keegan talks with Dr. Tanuja Chitnis about her paper on factors associated with recovery from acute optic neuritis in patients with multiple sclerosis. Dr. Adam Numis then reads the e-Pearl of the week about tanycytic ependymal tumors. In the next part of the podcast, Dr. Chenjie Xia focuses her interview with Dr. Karen Roos on neurology and infectious diseases such as bacterial meningoencephalitides.

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