Multiple Sclerosis Risk After Optic Neuritis

Final Optic Neuritis Treatment Trial Follow-up

The Optic Neuritis Study Group

Objective: To assess the risk of developing multiple sclerosis (MS) after optic neuritis and the factors predictive of high and low risk.

Design: Subjects in the Optic Neuritis Treatment Trial, who were enrolled between July 1, 1988, and June 30, 1991, were followed up prospectively for 15 years, with the final examination in 2006.

Setting: Neurologic and ophthalmologic examinations at 13 clinical sites.

Participants: Three hundred eighty-nine subjects with acute optic neuritis.

Main Outcome Measures: Development of MS and neurologic disability assessment.

Results: The cumulative probability of developing MS by 15 years after onset of optic neuritis was 50% (95% confidence interval, 44%-56%) and strongly related to presence of lesions on a baseline non–contrast-enhanced magnetic resonance imaging (MRI) of the brain. Twenty-five percent of patients with no lesions on baseline brain MRI developed MS during follow-up compared with 72% of patients with 1 or more lesions. After 10 years, the risk of developing MS was very low for patients without baseline lesions but remained substantial for those with lesions. Among patients without lesions on MRI, baseline factors associated with a substantially lower risk for MS included male sex, optic disc swelling, and certain atypical features of optic neuritis.

Conclusions: The presence of brain MRI abnormalities at the time of an optic neuritis attack is a strong predictor of the 15-year risk of MS. In the absence of MRI-detected lesions, male sex, optic disc swelling, and atypical clinical features of optic neuritis are associated with a low likelihood of developing MS. This natural history information is important when considering prophylactic treatment for MS at the time of a first acute onset of optic neuritis.

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OPTIC NEURITIS, AN ACUTE inflammatory disorder of the optic nerve, typically presents with sudden monocular visual loss and eye pain in young adults, more commonly in women. It is a common initial manifestation of multiple sclerosis (MS).[1] When optic neuritis occurs, brain magnetic resonance imaging (MRI) often demonstrates white-matter T2-weighted signal abnormalities consistent with demyelination (hereinafter referred to as lesions).[2] The Optic Neuritis Treatment Trial (ONTT) was a randomized trial that evaluated the use of corticosteroids in the treatment of acute optic neuritis. The ONTT showed that a 3-day course of methylprednisolone sodium succinate given intravenously in a dose of 250 mg every 6 hours followed by 2 weeks of oral prednisone in a dose of 1 mg/kg/d accelerated visual recovery but did not improve the eventual visual outcome.[3,4] Treatment with oral prednisone alone in a dose of 1 mg/kg/d for 2 weeks also did not improve visual outcome and was associated with an increased rate of optic neuritis recurrences. An unexpected finding was that those who received intravenous corticosteroids followed by oral corticosteroids had a temporarily reduced risk of development of a second demyelinating event consistent with MS during the first 2 years compared with subjects who received oral corticosteroids alone or placebo.[5]

The ONTT cohort has been followed up for 15 years. This report describes the results of the final examination, including the risk of developing MS after optic neuritis and factors predictive of high and low risk.

Table 1. Development of MS According to the Number of Lesions on Brain MRI at Study Entry

Lesions on Baseline MRI	No. of Patients	No. of Patients With MS	15-y Cumulative Probability of MS, %	HR (95% CI)
Overall	389[a]	157	50	
None	191	40	25	1 [Reference]
1	44	23	60	2.80 (1.68-4.68)
2	26	13	68	2.68 (1.43-5.00)
≥3	91	62	78	4.46 (2.99-6.65)

Abbreviations: CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging; MS, multiple sclerosis.
[a]Thirty-seven patients, including 19 with MS, did not have baseline MRI data.

METHODS

Written informed consent for study participation was obtained from all patients on ONTT entry and again before each follow-up phase. Institutional review board oversight remained in effect for each participating clinical center. Methods and earlier results have been described previously.[3,5-9] Pertinent details are summarized herein.

PATIENTS AND METHODS

Patients with acute unilateral optic neuritis were enrolled between July 1, 1988, and June 30, 1991, and randomly assigned to 1 of 2 corticosteroid regimens or placebo. Standardized unenhanced MRI of the brain (5-mm slices with a 2.5-mm gap using primarily 1.5-T scanners) was performed at enrollment, and the number of white matter lesions at least 3 mm in diameter was determined with standardized grading by a central reading center.[2] After the first year of follow-up, examinations were performed annually through 1997 and then again in 2001 through 2002 (hereinafter referred to as the 10-year examination). Telephone contact was maintained with consenting patients until 2006, when patients returned for reexamination. The 2006 examinations (hereinafter referred to as the 15-year examination) were performed at 1 of the 13 remaining ONTT centers when possible (2 original centers were no longer participating). Similar to previous examinations, this examination included a neurologic and an ophthalmologic assessment.

Diagnostic criteria for MS were based on the Poser clinical criteria for clinically definite MS[10] and consistent with the clinical criteria for MS that are part of the McDonald criteria diagnostic scheme.[11] Optic neuritis at study entry was considered 1 documented event. To meet MS diagnostic criteria, a patient had to have a clinical examination documenting a second new neurologic deficit attributable to central nervous system demyelination, consistent with neurologic symptoms lasting at least 24 hours and separated by at least 4 weeks from the initial optic neuritis event. Recurrent optic neuritis episodes in either eye were not considered in the diagnostic criteria for MS. Neurologic disability was assessed by a neurologist using the Kurtzke Functional Systems Scale and Expanded Disability Status Scale (EDSS).[12] The EDSS score was estimated from telephone interviews with 2 patients with MS who did not undergo a 15-year examination. Four patients who died of MS-related causes were assigned an EDSS score of 10.0.

STATISTICAL ANALYSES

The MS diagnosis date was the onset date of a second demyelinating event. For patients who did not develop MS, the last contact date (the most recent neurologic examination or, for those with no 15-year examination, a telephone assessment during which the patient reported no history consistent with development of MS) was used as the censoring date for analyses. We used life-table methods to compute the cumulative probability of developing MS within the intervals defined by the study's examination schedule (annual examinations during the first 5 years, the period after the 5- and through the 10-year examinations, and the period after the 10- and through the 15-year examinations). Cox proportional hazards modeling was used to assess baseline factors as potential predictors of MS separately for patients with and without lesions on baseline MRI. Hazard ratios of greater than 2.0, with 95% confidence intervals (CIs) not including 1.0, were considered suggestive of a meaningful association. The association of disability and number of lesions on baseline MRI was evaluated with the Spearman rank correlation test. Reported *P* values are 2-tailed. We used SAS statistical software (version 9.1; SAS Institute Inc, Cary, North Carolina) for analyses.

RESULTS

The study enrolled 389 patients with acute unilateral optic neuritis who were not diagnosed with probable or definite MS. Mean (SD) age at study entry was 32 (7) years; 77% were female and 85% were white.

DIAGNOSIS OF MS

The aggregate cumulative probability of developing MS by the 15-year examination was 50% (95% CI, 44%-56%) and was strongly related to the presence of lesions on the baseline brain MRI. That probability was 25% (95% CI, 18%-32%) for patients with no lesions and 72% (95% CI, 63%-81%) for patients with 1 or more lesions (**Table 1** and **Figure**). Four deaths attributable to MS occurred. Three of these patients had undergone baseline MRI, at which 1 had no lesions, 1 had 2 lesions, and 1 had more than 10 lesions. There was no appreciable difference in the risk of developing MS among the 3 original ONTT treatment groups (15-year cumulative probability [95% CI] of MS, 45% [34%-56%] in the intravenous corticosteroid group, 51% [40%-62%] in the oral corticosteroid group, and 53% [42%-64%] in the placebo group).

The risk of developing MS was highest in the first 5 years and then decreased, although the risk remained substantial throughout the 15 years of follow-up in patients who had lesions on baseline brain MRI. Among patients without MS at the 10-year examination, the probability of developing MS by the 15-year examination was 32% when 1 or more baseline lesions were present vs 2% when there were no baseline lesions (**Table 2**).

For the analysis of MS development, data were considered to be complete for 300 of the 389 patients (77%) (157 with MS, 136 without MS who completed the 15-year examination, and 7 who did not complete the examination but for whom telephone contact verified that no neurologic symptoms consistent with MS had occurred since the last examination). Among the remaining 89 patients, the median follow-up time was 5.2 years (interquartile range, 2.1-7.0 years). Twelve patients died of causes unrelated to MS. Four patients reported receiving immunomodulatory drugs, although they did not meet the study's diagnostic criteria for MS.

The predictive value of baseline factors for the development of MS varied depending on the presence or the absence of lesions on baseline brain MRI. When 1 or more lesions were present at study entry, no demographic or clinical characteristics were predictive of MS development (**Table 3**). In contrast, among patients without lesions, the risk of MS was higher for women when there was a history of a viral syndrome preceding the optic neuritis onset and when the optic disc appeared to be normal at the time of visual loss (retrobulbar neuritis).

Multiple sclerosis developed in 1 of 24 men (4%) with no lesions on the baseline brain MRI and optic disc swelling at onset of visual loss, compared with 9 of 57 women (16%) with these characteristics. Among patients with monofocal optic neuritis at study entry (no lesions on baseline brain MRI, no prior optic neuritis in the contralateral eye, and no prior neurologic symptoms or signs), MS did not develop in any patient when baseline ophthalmoscopy showed severe optic disc swelling (n=21), disc or peripapillary hemorrhages (n=16), or retinal macular exudates (n=8), when pain was absent (n=18), or when vision was reduced to no light perception (n=6).

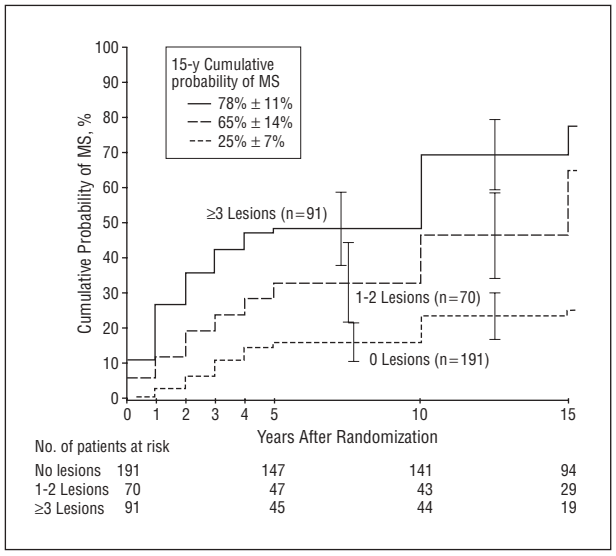

Figure. Life-table analysis of multiple sclerosis (MS) according to the number of lesions on baseline brain magnetic resonance imaging (MRI). Life-table intervals are defined by annual examinations during the first 5 years of the study and the periods after the 5- and through the 10-year examinations and after the 10- and through the 15-year examinations. The table under the horizontal axis represents the number of patients during follow-up who had not developed MS at the end of the previous interval. Patients with 1 or 2 lesions on MRI were combined into a single group because the rates of MS were similar.

NEUROLOGIC IMPAIRMENT AND DISEASE COURSE AMONG PATIENTS WITH MS

An EDSS score was available for 113 patients with MS who completed the 15-year examination, 4 patients who died of the effects of MS, and 2 patients for whom the EDSS score was estimated from a telephone interview. Among these patients, 66% had an EDSS score of less than 3 and 13% had an EDSS score of at least 6. Degree of disability was not related to the number of brain lesions on the baseline MRI scan (Spearman correlation coefficient ±95% CI, $r=0.07\pm0.19$) (**Table 4**). Among the 38 patients with MS for whom a current EDSS score was unavailable, median follow-up was 6 years (interquartile range, 5-8 years). At the last neurologic examination after MS diagnosis, the EDSS score for these patients was less than 3 in 25, 3 to less than 6 in 4, and at least 6 in 3 (6 had not had an EDSS assessment after being diagnosed as having MS). Among the 113 patients completing the examination, 67 (59%) reported current use of disease-modifying therapy, 26 (23%) reported use in the past but no current use, and 20

Table 2. Conditional Probability of Developing MS by Time Interval

Time Interval (No. of Patients)	Effective Sample Size[a]	No. of Patients		Conditional Probability of Developing MS, %
		Developed MS	Censored	
Overall (N=389)[b]				
0-5 Years	372.5	107	33	29
Year 6 through 10-year examination	221.0	38	56	17
After 10-year examination through 15-year examination	83.5	12	143	14
No lesions (n=191)				
0-5 Years	180.0	28	22	16
Year 6 through 10-year examination	123.0	11	36	9
After 10-year examination through 15-year examination	47.5	1	93	2
≥1 Lesion (n=161)				
0-5 Years	156.5	65	9	42
Year 6 through 10-year examination	79.5	24	15	30
After 10-year examination through 15-year examination	28.5	9	39	32

Abbreviations: MRI, magnetic resonance imaging; MS, multiple sclerosis.
[a] Calculated as the number of patients free of risk at the beginning of the interval minus half of the number of censored individuals and the cases of MS.
[b] Includes 37 patients with missing baseline MRI data.

Table 3. Baseline Factors Predictive of MS for Patients With Monofocal Optic Neuritis or With Optic Neuritis Associated With Lesions on Brain MRI[a]

	Monofocal Optic Neuritis[b]				≥1 Lesion on Baseline MRI			
Baseline Factor	No. of Patients	No. of Patients With MS	15-y Risk of MS, %	HR (95% CI)	No. of Patients	No. of Patients With MS	15-y Risk of MS, %	HR (95% CI)
Overall	179	35	24		161	98	72	
Sex								
Male	47	3	8	1 [Reference]	32	19	74	1 [Reference]
Female	132	32	29	3.57 (1.08-11.76)	129	79	72	0.89 (0.52-1.53)
Race[c]								
Black	18	2	14	1 [Reference]	25	13	78	1 [Reference]
White	156	33	25	1.63 (0.38-6.92)	135	85	72	1.51 (0.81-2.81)
Age, y								
>30.0	107	18	19	1 [Reference]	90	56	73	1 [Reference]
≤30.0	72	17	33	1.50 (0.76-2.94)	71	42	71	0.97 (0.63-1.49)
Family history of MS								
No	160	31	24	1 [Reference]	138	84	74	1 [Reference]
Yes	19	4	21	0.99 (0.34-2.87)	23	14	65	1.10 (0.59-2.03)
Preceding viral symptoms[d]								
No	127	19	18	1 [Reference]	124	79	76	1 [Reference]
Yes	52	16	38	2.42 (1.22-4.80)	37	19	54	0.75 (0.44-1.28)
Visual acuity in affected eye								
≥20/40	87	16	23	1 [Reference]	55	37	77	1 [Reference]
20/50-20/190	40	10	29	1.61 (0.72-3.61)	33	15	56	0.54 (0.28-1.02)
≤20/200	52	9	20	1.04 (0.45-2.38)	73	46	76	0.97 (0.61-1.56)
Optic disc appearance								
Edema	76	9	14	1 [Reference]	55	33	69	1 [Reference]
Normal	103	26	31	2.44 (1.13-5.26)	106	65	74	1.13 (0.72-1.77)
Presence of pain								
No	18	0	0	NA	12	7	71	1 [Reference]
Yes	161	35	26	NA	149	91	72	1.13 (0.49-2.58)

Abbreviations: CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging; MS, multiple sclerosis; NA, not applicable.
[a] Not included in either subgroup are 37 patients without a baseline MRI scan of the brain and 12 patients with no lesions on the baseline MRI scan who reported prior nonspecific neurologic symptoms suggestive of demyelination or prior optic neuritis in the contralateral eye.
[b] This group was defined as patients with no lesions on brain MRI, no prior self-reported nonspecific neurologic symptoms (insufficient for a diagnosis of MS), and no prior optic neuritis in the contralateral eye.
[c] Six patients of other races are not listed (5 with monofocal optic neuritis and 1 with ≥1 lesion).
[d] Indicates self-reported viral symptoms in the 4 weeks before study entry.

(18%) reported no current or past use. The use of disease-modifying therapy among subjects with and without lesions on the baseline brain MRI was similar.

COMMENT

A relationship between optic neuritis and MS has been well recognized for many years. In this longitudinal study, the 15-year risk of developing MS was 50% based on clinical criteria alone. The risk was strongly related to MRI evidence of prior demyelination in the white matter of the brain at the time of optic neuritis onset (25% when no lesions were present and 72% when lesions were present). When at least 1 lesion was present, the risk was fairly consistent throughout the 15 years and did not substantially increase when additional lesions were present. For patients without brain lesions at onset, the risk of MS was greatest in the first 5 years, and if MS did not develop in the first 10 years, the risk during the period between the 10- and 15-year examinations approached 0; only 1 patient without lesions at study entry developed MS during the period between the 10- and 15-year examinations.

Regardless of whether lesions were present on brain MRI at the time of the optic neuritis episode, neurologic disability was mild in most patients who developed MS. However, because treatment of MS was not controlled in the study and most patients who developed MS were treated with disease-modifying therapies, we could not determine the degree of disability that occurs without treatment.

There was a clear distinction in the risk profile between patients with and without evidence of prior demyelination on brain MRI (≥1 lesion). Patients with abnormal brain MRI findings already have morphologic evidence of disseminated disease and could be considered to have MS at the time of the optic neuritis episode. Thus, it is not surprising that we did not identify any factors modifying the risk of MS in this group. In contrast, among patients with normal brain MRI findings, 2 subsets may exist, one destined to have MS and the other with a non–MS-related process of unknown cause.

Among patients without lesions on baseline brain MRI, the risk of MS was 3 times higher in women, consistent with the well-described sex predilection of MS. In addition, MS was more than twice as likely to develop when optic neuritis affected the retrobulbar part of the optic nerve rather than the anterior optic nerve, consistent with the common belief that retrobulbar neuritis is the typical form of

optic neuritis in MS. Men with anterior optic neuritis had a lower risk of MS, whereas both sexes had a low risk when atypical features of the optic neuritis were present, namely, no light perception in the affected eye, absence of periocular pain, and ophthalmoscopic findings of severe optic disc swelling, peripapillary hemorrhages, or retinal exudates.

Our finding of a 50% 15-year risk of MS after optic neuritis is similar to several previous reports[13-15] and lower than others[16-18]; however, all previous series had smaller sample sizes. Differences in risk estimates across studies also may be attributable to differences in patient inclusion criteria, retention rates, and diagnostic criteria for MS. The most similar study included 71 patients who presented with an acute demyelinating syndrome, 36 (51%) of whom had optic neuritis.[16] During a mean follow-up of 14.1 years, clinically definite MS developed in 4 of 21 patients (19%) with normal brain MRI findings at study entry and in 44 of 50 patients (88%) with an abnormal finding. That study found, as we did, that, once there was at least 1 lesion on brain MRI, more lesions did not appreciably affect long-term risk of MS.

Our finding of a low frequency of substantial disability among patients who developed MS is similar to some previous studies[13,19] but not others.[16,20] Unlike Brex et al,[16] we found that the number of lesions on baseline brain MRI was not associated with the degree of disability. In our study, moderate or severe disability was present in 39% of patients with no baseline lesions and in 31% of patients with 1 or more lesions. Because the reported use of disease-modifying therapy among subjects with and without brain lesions on MRI scans was similar, it is unlikely that the difference in severe disability between these 2 groups can be attributed to a higher rate of treatment among those with lesions. Previous studies have reported that the MS course is more benign when the initial event is optic neuritis rather than a brainstem or spinal cord syndrome.[21,22] Thus, differences in results between our study and that of Brex et al[16] may be related to the fact that patients with optic neuritis constituted only 50% of their study cohort.

Eligibility criteria were sufficiently broad that our results should be applicable to most patients presenting with optic neuritis as a first demyelinating event. Having incomplete data for 23% of the cohort is unlikely to be a source of appreciable bias because most of these patients completed at least 5 years of follow-up. Because few patients without MS in our study were treated prophylactically with immunomodulatory drugs, our risk estimate is not biased by use of therapies that have become available since the study began. One important factor to consider in interpreting our results is the technologic MRI advances that have occurred since the initiation of our study in 1988. Current imaging techniques are more sensitive in the detection of demyelination and might distinguish the risk of MS according to the presence or absence of MRI abnormalities to an even greater extent than we found. Current diagnostic criteria for MS permit dissemination of demyelinative lesions in time to be documented with MRI in lieu of a second clinical event.[11]

Our results are important to clinicians in several respects. They reaffirm the prognostic value of a brain MRI at the time of a first episode of optic neuritis because presence of even a single lesion more than doubles the future risk of MS. Patients with abnormal brain MRI findings at the time of optic neuritis continue to be at substantial risk for the development of MS, even if they have not developed MS within 10 years after onset of optic neuritis. The very low risk of MS when atypical features of optic neuritis are present highlights the importance of an ophthalmologic examination to identify these features, particularly for patients with normal brain MRI findings. With normal brain MRI findings, MS is extremely unlikely to develop more than 10 years after the initial optic neuritis episode. Although our follow-up is only 15 years, it seems reasonable to conclude that the future risk for these patients will remain exceedingly low. Among patients who develop MS, most will follow a relatively benign neurologic course for many years.

The initiation of prophylactic treatment for MS at the time of an optic neuritis episode or of another first demyelinating event is controversial.[23,24] Although our study cannot define which patients may benefit from prophylactic treatment, the results certainly justify withholding treatment in patients with a typical first episode of acute monosymptomatic optic neuritis who have a normal brain MRI finding because many may never develop MS. For patients with an abnormal brain MRI finding at the time of a first attack of optic neuritis, one must

Table 4. Neurologic Disability at the 15-Year Examination Among Patients With MS According to Number of Lesions on Brain MRI at Baseline[a]

	No. (%) of Patients			
		No. of Lesions on Baseline MRI		
EDSS Score	Total (N=105)	None (n=28)	1 (n=21)	≥2 (n=56)
0	17 (16)	3 (11)	7 (33)	7 (13)
1	14 (13)	4 (14)	3 (14)	7 (13)
1.5	8 (8)	2 (7)	1 (5)	5 (9)
2	22 (21)	5 (18)	4 (19)	13 (23)
2.5	9 (9)	3 (11)	3 (14)	3 (5)
3	9 (9)	3 (11)	0	6 (11)
3.5	9 (9)	5 (18)	0	4 (7)
4	1 (1)	0	0	1 (2)
4.5	0	0	0	0
5	1 (1)	1 (4)	0	0
5.5	2 (2)	0	0	2 (4)
6	2 (2)	0	2 (10)	0
6.5	4 (4)	0	0	4 (7)
7	1 (1)	0	0	1 (2)
7.5	1 (1)	1 (4)	0	0
8	1 (1)	0	1 (5)	0
8.5	0	0	0	0
9	1 (1)	0	0	1 (2)
9.5	0	0	0	0
10	3 (3)	1 (4)	0	2 (4)
<3	70 (67)	17 (61)	18 (86)	35 (63)
≥3	35 (33)	11 (39)	3 (14)	21 (38)
≥6	13 (12)	2 (7)	3 (14)	8 (14)

Abbreviations: EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis.

[a] Fourteen cases of MS were excluded because of missing baseline MRIs. Of the remaining 105, EDSS scores for 100 patients were from the 15-year examination, 3 were imputed from death related to MS, and 2 were imputed from telephone interviews. For between-group comparisons, Spearman correlation ±95% confidence interval = 0.07 ± 0.19.

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balance their risk of developing MS with the potential adverse effects and cost of disease-modifying agents. Treatment may be appropriate, but that decision must be made on an individual basis for each patient, with consideration given to the results of additional ancillary testing.

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