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The 5-year risk of MS after optic neuritis

Experience of the Optic Neuritis Treatment Trial

Optic Neuritis Study Group*

Article abstract—The objective of our study was to assess the 5-year risk of and prognostic factors for the development of clinically definite multiple sclerosis (CDMS) following optic neuritis. In a prospective cohort study design, 388 patients, who did not have probable or definite MS at study entry enrolled in the Optic Neuritis Treatment Trial between 1988 and 1991, and were followed for the development of CDMS. The 5-year cumulative probability of CDMS was 30% and did not differ by treatment group. Neurologic impairment in the patients who developed CDMS was generally mild. Brain MRI performed at study entry was a strong predictor of CDMS, with the 5-year risk of CDMS ranging from 16% in the 202 patients with no MRI lesions to 51% in the 89 patients with three or more MRI lesions. Independent of brain MRI, the presence of prior nonspecific neurologic symptoms was also predictive of the development of CDMS. Lack of pain, the presence of optic disk swelling, and mild visual acuity loss were features of the optic neuritis associated with a low risk of CDMS among the 189 patients who had no brain MRI lesions and no history of neurologic symptoms or optic neuritis in the fellow eye. The 5-year risk of CDMS following optic neuritis is highly dependent on the number of lesions present on brain MRI. However, even a normal brain MRI does not preclude the development of CDMS. In these patients with no brain MRI lesions, certain clinical features identify a subgroup with a particularly low 5-year risk of CDMS.

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The Optic Neuritis Treatment Trial (ONTT), funded by the National Eye Institute of the National Institutes of Health, assessed the efficacy of corticosteroids as treatment for optic neuritis. A secondary objective was to investigate the relationship between optic neuritis and MS. The cohort of patients who did not have MS at the time of study entry has now been followed for 5 years. After 2 years of follow-up we reported that MRI was a strong predictor of the early risk of MS and that treatment with intravenous followed by oral corticosteroids transiently reduced the rate of new MS attacks.[1] We now report the 5-year risk of MS, prognostic factors for the development of MS, and the degree of neurologic disability among the patients developing MS.

Methods. Fifteen clinical centers in the United States enrolled 457 patients between July 1, 1988, and June 30,

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1991, according to a previously reported protocol approved by investigational review boards.[1-4] The criteria for entry into the ONTT included the diagnosis of acute unilateral optic neuritis with visual symptoms of 8 days or less, age between 18 and 46 years, no previous history of optic neuritis or ophthalmoscopic signs of optic atrophy in the affected eye, no evidence of a systemic disease other than MS that might be associated with the optic neuritis, and no previous treatment with corticosteroids for optic neuritis in the fellow eye or for MS.

Because the primary objective of the current follow-up study was to evaluate risk factors for the development of clinically definite MS (CDMS) in patients with monofocal optic neuritis, we excluded from analysis 66 patients (14%) from the original cohort who were diagnosed as having either CDMS (n = 36) or probable MS (n = 30) on study entry. Also excluded were two patients determined subsequent to study entry not to have optic neuritis (one with an ophthalmic artery aneurysm and the other with a pituitary tumor) and one patient who withdrew before having a baseline neurologic examination. These exclusions reduced the cohort for the current study to 388 patients.

Treatment of optic neuritis. Each patient received one of three randomly assigned treatment regimens at the time of study enrollment: (1) intravenous methylprednisolone (250 mg every 6 hours for 3 days) followed by oral prednisone (1 mg/kg per day for 11 days) (referred to as the intravenous group), (2) oral prednisone (1 mg/kg per day for 14 days) (referred to as the prednisone group), or (3) oral placebo (for 14 days) (referred to as the placebo group). Regimens 1 and 2 were followed by a short oral dosage taper consisting of 20 mg of prednisone on day 15 and 10 mg on days 16 and 18. Through randomization, 126 patients were assigned to the placebo group, 133 to the intravenous group, and 129 to the prednisone group.

Baseline evaluations and determination of outcome. On study entry, patients underwent ophthalmic and neurologic examinations, visual function testing, and brain MRI by standardized protocols. Follow-up protocol neurologic examinations were performed after 6 and 12 months, and then yearly. In addition, formal phone contact with each patient was made twice a year to obtain updated medical information. Attempts were made (by letter or telephone if the patient was unwilling to have an examination) to contact all living patients who missed the 5-year follow-up visit to obtain medical information.

At each follow-up visit a structured neurologic examination, including an assessment of neurologic disability using the Expanded Disability Status Scale (EDSS)[5], and visual function testing (visual acuity, contrast sensitivity, visual field, and color vision) were performed. The patient's MS status was classified as no, possible, probable, or definite based solely on the clinical criteria.

A demyelinating attack was defined as a patient-reported episode of symptoms attributable to acute demyelination in one or more regions of the CNS lasting more than 24 hours and separate from a previous attack by at least 4 weeks.[6] Patients were diagnosed as having CDMS when a second attack (in addition to the optic neuritis at the time of study entry) was confirmed by an examination that detected a new neurologic abnormality. Patients were classified as probable MS when symptoms consistent with a new demyelinating event occurred for which there was not a confirmatory examination demonstrating a new neurologic abnormality. For the purposes of this study, patients who reported neurologic symptoms but did not fulfill the criteria for an attack were classified as possible MS, and patients whose only clinical event was the optic neuritis at study entry were classified as no MS. Recurrent episodes of optic neuritis in either eye were not considered in the diagnostic criteria for MS. All neurologic examination forms were evaluated by a blinded reviewer to verify that the criteria had been properly applied in classifying the patients' MS status.

Unenhanced MRI performed at study entry on 351 of the 388 patients was classified by a reading center using a blinded grading system.[7] Because contrast-enhanced MRI was not in widespread use at the time the study was initiated, it was not included in the MRI protocol. As previously detailed,[7] each signal abnormality was characterized by its size (greater than or less than 3 mm), location (periventricular or nonperiventricular), and shape (ovoid or nonovoid). For purposes of this article, brain MRI "lesions" refer to signal abnormalities at least 3 mm in size.

Completeness of follow-up. Five or more years of follow-up were completed by 341 of the 388 patients (88%). For 11 of the 341, the 5-year examination was performed by a nonstudy neurologist because returning to an ONTT clinical center was not feasible. Eight of the 47 patients with fewer than 5 years of follow-up (*noncompleters*) had been diagnosed as CDMS at their last completed study visit, one of whom died of pulmonary complications related to severe MS. Among the other 39 noncompleters, one died of suicide, and current medical information was available via telephone contact with 16 others. Fifteen of the 16 contacted patients reported no symptoms suggestive of a neurologic event. One patient whose diagnosis was probable MS at the last completed study examination reported symptoms consistent with a sensory exacerbation. The noncompleters were more likely to be African-American ($p = 0.0003$) and male ($p = 0.027$), but were otherwise similar to the completers of 5 or more years of follow-up (table 1).

Statistical analysis. The assumptions used in the sample size calculation were based on assessing the efficacy of corticosteroids on visual recovery as described previously.[4] All reported p values are two tailed.

Cumulative probabilities of the development of CDMS were calculated with Kaplan-Meier estimates. The treatment groups were compared with the Mantel log rank test.[8] Unadjusted and adjusted rate ratios for the development of CDMS were determined from a proportional hazards model.[9] Risk indicators for CDMS were assessed separately for patients with abnormal brain MRI and for patients with monofocal optic neuritis (no brain MRI lesions and no prior history of either nonspecific neurologic symptoms or optic neuritis in the fellow eye). Risk indicators for CDMS were not assessed separately by treatment group because the 5-year risk of MS was similar between treatment groups and there is no physiologic reason to believe that interaction exists between risk indicators and treatment.

Results. Clinically definite MS developed within 5 years in 106 of the 388 patients (27%), and probable MS developed in an additional 35 patients (9%). The 5-year cumula-

Table 1 Comparison of completers and noncompleters of 5-year neurologic examination

Characteristic at study entry	Total (n = 388)	Completers* (n = 341)	Noncompleters† (n = 47)	*p* Value‡
Age (mean ± SD)	32 ± 7	32 ± 7	31 ± 5	.26
Gender, n (%) female	299 (77%)	269 (79%)	30 (64%)	.027
Race, n (%)				
Caucasian	330 (85%)	298 (87%)	32 (68%)	—
African-American	50 (13%)	35 (10%)	15 (32%)	.0002
Other	8 (2%)	8 (2%)	0	
Treatment group distribution, n (%)				
Placebo	126 (33%)	111 (33%)	15 (32%)	1.0
Intravenous	133 (34%)	111 (33%)	22 (47%)	.070
Prednisone	129 (33%)	119 (35%)	10 (21%)	.070
Brain MRI, n (%)				
No lesions	202 (52%)	179 (52%)	23 (49%)	.87
1–2 lesions	60 (16%)	54 (16%)	6 (13%)	—
≥3 lesions	89 (23%)	77 (23%)	12 (26%)	
No MRI data	37 (10%)	31 (9%)	6 (13%)	—
Prior nonspecific neurologic symptoms, n (%)	65 (17%)	59 (17%)	6 (13%)	.54
Visual acuity in affected eye:	20/63	20/63	20/80	.58
Median (quartiles)	(5/160, 20/25)	(5/160, 20/25)	(5/200, 20/25)	—

* Completed 5 or more years of follow-up.
† Completed less than 5 years of follow-up: 4 years completed, four patients; 3 years, seven patients; 2 years, eight patients; 1 year, nine patients, <1 year, 19 patients.
‡ From Fisher's exact test for categorical variables and Wilcoxon's rank sum test for continuous variables.

tive probability of CDMS was 30% and of probable or definite MS was 40%.

Treatment had no statistically significant effect on the 5-year development of MS. The cumulative probability of developing CDMS within 5 years was 31% in the placebo group, 27% in the intravenous group, and 32% in the prednisone group (by life table analysis; compared with the placebo group, $p = 0.38$ for the intravenous group and $p = 0.85$ for the prednisone group) (figure 1).

Factors predictive of the development of CDMS. Aggregate analysis. The presence of signal abnormalities on brain MRI performed at the time of optic neuritis was the single most important predictor of the development of CDMS by 5 years (figure 2, table 2). The probability of CDMS ranged from 16% in the 202 patients with no brain MRI lesions to 51% in the 89 patients with three or more lesions.

Independent of brain MRI, the presence of prior nonspecific neurologic symptoms (predominantly paresthesias of short duration) was also associated with the development of CDMS (adjusted for MRI grade; rate ratio, 2.22; 95% CI, 1.45 to 3.40). Among the 202 patients with no brain MRI

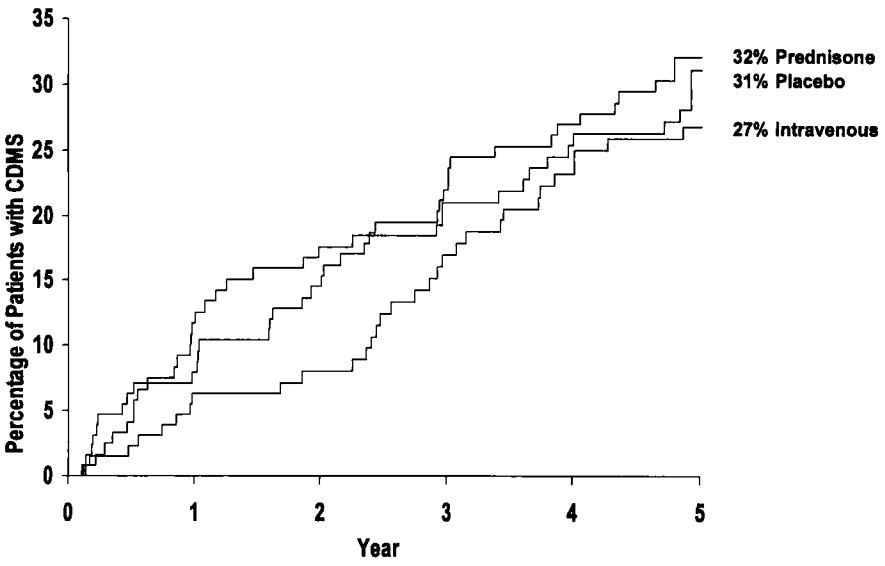

Figure 1. Kaplan-Meier curves showing cumulative probability of clinically definite MS (CDMS) according to treatment group. By the Mantel log rank test p = *0.38, comparing the intravenous group with the placebo group; and* p = *0.85, comparing the prednisone group with the placebo group.*

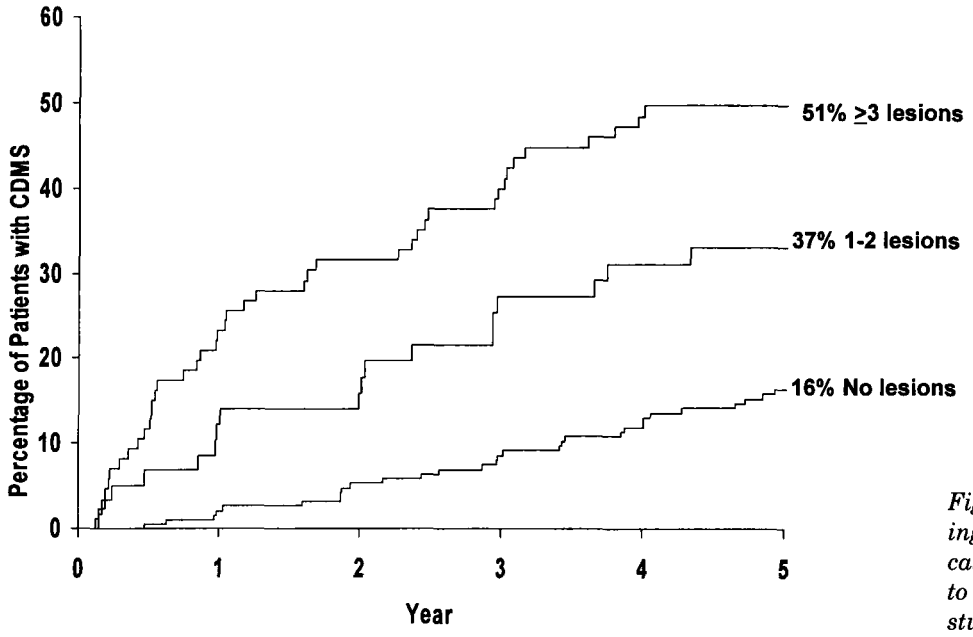

Figure 2. Kaplan-Meier curves showing cumulative probability of clinically definite MS (CDMS) according to the number of MRI lesions at study entry.

lesions, the probability of developing CDMS within 5 years was 44% in the 12 patients who reported prior nonspecific neurologic symptoms as compared with only 15% in the 190 patients who did not report such symptoms (p = 0.002).

Abnormal brain MRI. Among the 149 patients with brain MRI lesions, CDMS developed in 63 patients (42%). Prior nonspecific neurologic symptoms and prior optic neuritis in the fellow eye were the only factors associated with an increased 5-year risk of MS in these patients (table 3).

When brain MRI lesions and prior nonspecific neurologic symptoms were both present, the risk of CDMS was high. Among the patients reporting prior nonspecific neurologic symptoms, the 5-year probability of CDMS was 43% in the 19 patients with one or two MRI lesions and 66% in the 26 patients with three or more lesions.

No brain MRI lesions and absence of prior neurologic symptoms and fellow eye optic neuritis ("monofocal optic neuritis"). We separately assessed factors associated with the development of CDMS among the 189 patients who had no brain MRI lesions and no prior neurologic symptoms or optic neuritis in the fellow eye. In this subgroup, which could be considered to have monofocal optic neuritis, CDMS developed within 5 years in only 25 patients (13%), and was more likely in women (rate ratio, 2.03; 95% CI, 0.59 to 7.03) and in Caucasians (rate ratio, 2.07; 95% CI, 0.45 to 9.65). However, because of the small number of men and non-Caucasians, the CIs are wide and we cannot be certain of a true association. Age did not appear to be an important predictive factor. A patient-reported viral syndrome occurring within the month prior to optic neuritis also was associated with the development of CDMS (rate ratio, 3.32; 95% CI, 1.42 to 7.76) (table 4).

In this group of patients with monofocal optic neuritis, three clinical features were associated with a particularly low risk of CDMS: lack of pain, the presence of optic disk swelling, and mild visual acuity loss (see table 4). CDMS developed by 5 years in none of the 19 patients whose visual loss was painless, eight of the 90 patients (9%) whose visual acuity at study entry was 20/40 or better, and in six of the 78 patients (8%) who had a swollen optic disk. Among the patients with a swollen disk, CDMS did not develop in any patient who had severe disk edema (n =

Table 2 *Development of MS within 5 years according to MRI grade*

Brain MRI at study entry	n	Definite MS		Probable or definite MS	
		Cumulative probability (%)	Rate ratio (95% CI)*	Cumulative probability (%)	Rate ratio (95% CI)*
No lesions†	202	16	1.0	24	1.0
1 lesion	36	44	3.02 (1.60–5.70)	55	2.88 (1.66–4.99)
2 lesions	24	26	1.99 (0.83–4.78)	49	2.62 (1.35–5.08)
≥3 lesions	89	51	4.44 (2.79–7.09)	63	4.15 (2.78–6.20)
Missing‡	37	40	2.70 (1.41–5.18)	46	2.16 (1.20–3.88)
Total	388	30	—	40	—

* From the proportional hazards model. Compared with rate in patients with no lesions.
† Includes 163 patients with a normal scan and 39 patients with either punctate signal abnormalities (<3 mm) or nonspecific changes.
‡ Patients who did not have an MRI performed or for whom the MRI was not according to protocol and could not be graded.

Table 3 *Factors predictive of development of clinically definite MS (CDMS) within 5 years in 149 patients with abnormal brain MRI*

Predictive factors*	n	n (%) with CDMS by 5 years	Unadjusted rate ratio (95% CI)†	Adjusted rate ratio (95% CI)‡
Total	149	63 (42)	—	—
Gender				
Male	31	15 (48)	1.0	1.0
Female	118	48 (41)	0.78 (0.44–1.40)	0.77 (0.40–1.47)
Race				
African-American	23	6 (26)	1.0	1.0
Caucasian	125	57 (46)	1.83 (0.79–4.25)	1.85 (0.77–4.48)
Other	1	0	—	—
Age				
>30 y	86	36 (42)	1.0	1.0
≤30 y	63	27 (43)	1.11 (0.68–1.84)	1.05 (0.61–1.81)
Prior neurologic symptoms				
No	104	39 (38)	1.0	1.0
Yes	45	24 (53)	1.68 (1.01–2.80)	1.71 (0.97–3.01)
Prior fellow eye optic neuritis				
No	140	58 (41)	1.0	1.0
Yes	9	5 (56)	3.07 (1.22–7.76	2.09 (0.72–6.09)
Family history of MS				
No	127	51 (40)	1.0	1.0
Yes	22	12 (55)	1.62 (0.86–3.04)	1.46 (0.73–2.93)
Prior viral syndrome§				
No	117	49 (42)	1.0	1.0
Yes	32	14 (44)	1.01 (0.56–1.83)	0.98 (0.49–1.95)
Season of onset				
Summer (Jun–Aug)	36	15 (42)	1.0	1.0
Autumn (Sep–Nov)	41	20 (49)	1.43 (0.73–2.79)	1.33 (0.65–2.70)
Winter (Dec–Feb)	34	14 (41)	0.90 (0.43–1.87)	0.70 (0.32–1.50)
Spring (Mar–May)	38	14 (37)	0.79 (0.38–1.64)	0.82 (0.38–1.74)
Years living in the North in first 15 years of life¶				
<10 y	50	19 (38)	1.0	1.0
≥10 y	99	44 (44)	1.17 (0.68–2.00)	1.10 (0.60–2.01)
Visual acuity at entry				
≥20/40	51	23 (45)	1.0	1.0
20/50–20/190	29	10 (34)	0.76 (0.36–1.61)	0.89 (0.41–1.94)
≤20/200	69	30 (43)	1.09 (0.63–1.87)	1.32 (0.73–2.40)
Optic disk appearance				
Edema	53	20 (38)	1.0	1.0
Normal	96	43 (45)	1.26 (0.74–2.14)	1.30 (0.75–2.26)
Pain#				
No	11	5 (45)	1.0	1.0
Yes	138	58 (42)	0.93 (0.37–2.32)	0.82 (0.31–2.18)

* Other variables that were assessed but were not found to be predictive included ANA blood level, pattern of visual field defect in the affected eye, and presence of a visual field defect in the fellow eye.
† From the proportional hazards model with a single exposure variable (or with dummy variables as indicated).
‡ From the proportional hazards model including all variables. Race is included in the model as Caucasian versus non-Caucasian.
§ From a patient report of having experienced a viral syndrome in the prior month.
¶ North is defined as the states predominately located above latitude 40° north.
# Occurring in association with optic neuritis at study entry.
1.0 = Referent level.

Table 4 *Factors predictive of development of clinically definite MS (CDMS) within 5 years in 189 patients with no brain MRI lesions and no prior history of neurologic symptoms or fellow eye optic neuritis ("monofocal optic neuritis")*

Predictive factors*	n	n (%) with CDMS by 5 years	Unadjusted rate ratio (95% CI)†	Adjusted rate ratio (95% CI)‡
Total	189	25 (13)	—	—
Gender				
Male	48	3 (6)	1.0	1.0
Female	141	22 (16)	2.24 (0.67–7.49)	2.03 (0.59–7.03)
Race				
African-American	19	2 (11)	1.0	1.0
Caucasian	165	23 (14)	1.20 (0.28–5.09)	2.07 (0.45–9.65)
Other	5	0	—	—
Age				
>30 y	110	14 (13)	1.0	1.0
≤30 y	79	11 (14)	1.12 (0.51–2.47)	1.06 (0.46–2.42)
Family history of MS				
No	169	22 (13)	1.0	1.0
Yes	20	3 (15)	1.07 (0.32–3.57)	1.72 (0.48–6.23)
Prior viral syndrome§				
No	133	12 (9)	1.0	1.0
Yes	56	13 (23)	2.87 (1.31–6.28)	3.32 (1.42–7.76)
Season of onset				
Summer (Jun–Aug)	44	6 (14)	1.0	1.0
Autumn (Sep–Nov)	50	8 (16)	1.19 (0.41–3.42)	1.22 (0.41–3.63)
Winter (Dec–Feb)	43	4 (9)	0.69 (0.20–2.45)	0.55 (0.14–2.12)
Spring (Mar–May)	52	7 (13)	1.14 (0.38–3.40)	1.80 (0.56–5.76)
Years living in North in first 15 years of life¶				
<10 y	95	14 (15)	1.0	1.0
≥10 y	94	11 (12)	0.79 (0.36–1.73)	0.65 (0.29–1.45)
Visual acuity at entry				
≥20/40	90	8 (9)	1.0	1.0
20/50–20/190	44	8 (18)	2.27 (0.85–6.06)	2.95 (0.95–9.19)
≤20/200	55	9 (16)	1.92 (0.74–4.98)	2.38 (0.85–6.67)
Optic disk appearance				
Edema#	78	6 (8)	1.0	1.0
Normal	111	19 (17)	2.43 (0.97–6.09)	2.38 (0.91–6.20)
Pain**				
No	19	0	—	—
Yes	170	25 (15)	—	—

* Other variables that were assessed but were not found to be predictive included ANA blood level, pattern of visual field defect in the affected eye, and the presence of a visual field defect in the fellow eye.
† From the proportional hazards model with a single exposure variable (or with dummy variables as indicated).
‡ From the proportional hazards model including all variables. Race is included in the model as Caucasian versus non-Caucasian.
§ From a patient report of having experienced a viral syndrome in the prior month.
¶ North is defined as the states predominately located above latitude 40° north.
1.0 = Referent level.
# CDMS developed in six of the 57 patients (10.5%) with mild disk edema and in none of the 21 patients with severe disk edema.
** Occuring in association with optic neuritis at study entry.

21), disk or peripapillary hemorrhage (n = 16), or macular exudates (n = 8). Patients with severe disk edema followed a course consistent with optic neuritis.

Neurologic impairment. Neurologic impairment was generally mild after 5 years even in those patients who had developed CDMS by that time (table 5). Only 13 of the

Table 5 Neurologic disability (EDSS) after 5 years for patients who developed clinically definite MS according to the number of brain MRI lesions on study entry

	MRI grade				
EDSS Score	Total (n =105)* n (%)	None (n = 30) n (%)	1–2 (n = 20) n (%)	≥3 (n = 42) n (%)	No MRI data (n = 13) n (%)
0.0	33 (31)	10 (33)	7 (35)	12 (29)	4 (31)
1.0	20 (19)	5 (17)†	3 (15)	9 (21)	3 (23)
1.5	15 (14)	5 (17)	4 (20)	3 (7)†	3 (23)
2.0	15 (14)	6 (20)	4 (20)	5 (12)†	0
2.5	5 (5)	2 (7)	0	3 (7)	0
3.0	7 (7)	0	1 (5)	5 (12)†	1 (8)
3.5	2 (2)	1 (3)	1 (5)	0	0
4.0	1 (1)	0	0	1 (2)†	0
4.5	0	0	0	0	0
5.0	0	0	0	0	0
5.5	2 (2)	0	0	2 (5)	0
6.0	2 (2)	0	0	1 (2)	1 (8)
6.5	1 (1)	0	0	1 (2)	0
7.5	1 (1)	0	0	0	1 (8)†
10.0	1 (1)	1 (3)†	0	0	0

* For one patient who had more than three MRI lesions, there was no available information to estimate the EDSS score.
† Includes one patient who missed the 5-year visit, for whom the EDSS score was estimated based on available information (see text).

EDSS = Expanded Disability Status Scale.

98 patients (13%) with CDMS, 3% of the entire cohort, who completed at least 5 years of follow-up had moderate or severe disability (EDSS score ≥3.0). However, among the eight patients who were diagnosed with CDMS but who did not complete 5 years of follow-up, one died from complications related to severe MS, as noted earlier. Based on available information from medical records and telephone contacts with six of the other seven patients, moderate or severe disability was estimated to be present in three of these patients. Adding these patients to the analysis increases the number of patients with moderate or severe disability to 17 patients, which represents 16% of those who developed CDMS and 4% of the entire cohort.

Visual loss contributed little to the disability score of most patients. Among the 98 patients who developed CDMS within 5 years and completed the 5-year examination, visual acuity in the worse eye was ≥20/20 in 74%, 20/25 to 20/40 in 14%, 20/50 to 20/190 in 5%, and 20/200 or worse in 6%. Visual acuity in the better eye was ≥20/20 in 91%, 20/25 to 20/40 in 6%, 20/50 to 20/190 in 1%, and 20/200 or worse in 2%.

Among the 16 living patients whose EDSS score was ≥3.0, nearly all patients had some motor weakness, ataxia, hypesthesia, and urinary urgency/frequency. Three patients had mild cognitive deficits. Nine patients were fully ambulatory, two had limited but unassisted ambulation, three had limited and intermittently assisted ambulation, one had limited and constantly assisted ambulation, and one was nonambulatory.

Among the patients developing CDMS, those who had more brain MRI lesions at the time of study entry were at greater risk for neurologic disability (see table 5). Only two of 30 patients (7%) with no brain MRI lesions developed moderate or severe disability (EDSS score ≥3.0) compared with 10 of 42 patients (24%) who had three or more lesions ($p = 0.063$). Of the 14 patients with an available MRI grading who developed moderate or severe disability (EDSS score ≥3.0), 10 had three or more lesions on MRI, two had one to two lesions, and two had no lesions. However, the one patient who died from MS had no lesions on the baseline MRI.

There was no difference in the degree of neurologic disability across treatment groups. Among the patients with CDMS within 5 years, moderate or severe disability (EDSS score, ≥3.0) was present in 5 of 35 patients (14%) in the placebo group, 5 of 31 patients (16%) in the intravenous group, and 7 of 39 patients (18%) in the prednisone group ($p = 0.95$).

Systemic diseases. One patient was diagnosed to have sarcoidosis that presumably was the cause of the optic neuritis at study entry. No other patients developed a systemic disease other than MS that could be associated with optic neuritis.

Discussion. Within our cohort of 388 patients followed from the onset of an acute episode of optic neuritis, the 5-year risk of development of CDMS based strictly on conventional clinical criteria was 30%. When CDMS did develop, neurologic disability was mild in most patients.

The presence of brain MRI lesions at the time of study entry was the strongest predictor of the development of CDMS by 5 years. However, even when

there were no brain MRI lesions at study entry, the 5-year risk of CDMS was sufficiently high (16%) that a normal brain MRI should not be taken to signify that CDMS will not develop. A prior history of neurologic symptoms and a history of optic neuritis in the fellow eye were also associated with development of CDMS. By contrast there were certain clinical features associated with a reduced risk of developing CDMS in patients with apparently monofocal optic neuritis (no brain MRI lesions and no prior history of neurologic symptoms or optic neuritis in the fellow eye): lack of pain, presence of optic disk edema (particularly if severe or associated with hemorrhage or exudate), and presence of mild visual loss.

There were no significant differences among treatment groups in either the rate of development of CDMS or in the degree of neurologic disability among those patients who had developed CDMS at the end of 5 years of follow-up. The observed, decreased 2-year rate of CDMS in patients treated with intravenous followed by oral corticosteroids, which we had previously reported,[1] abated in the third year of follow-up. As discussed in a separate publication,[10] we believe that this transient reduction in the rate of development of CDMS was a real effect of intravenous corticosteroid treatment and unlikely to be due to bias, confounding, or chance.

We believe our results to have high validity and, based on the patient enrollment criteria, to have applicability to most patients presenting with optic neuritis as a first demyelinating event. Our sample size was large and our follow-up rate (88% with completed 5-year examinations and an additional 5% with current medical information) was high for a longitudinal study such as this. Nevertheless, it is likely that our life table calculation of a 30% 5-year probability of CDMS is a slight overestimate, based on the information collected during telephone contact with patients who did not complete the 5-year examination, which suggests that few if any of the patients not diagnosed as CDMS at their last completed examination experienced a neurologic event sufficient for a diagnosis of CDMS. On the other hand, our calculation of the incidence of moderate or severe disability in the patients who developed CDMS is likely to be a slight underestimate when based solely on the completed 5-year examination data. There is no reason to believe that incomplete follow-up would bias the assessments of the relative importance of prognostic factors.

Comparing our results with those of other studies is difficult because no other reported study has a cohort of equivalent size and follow-up. Other studies have reported approximately a 40% 5-year risk of MS after optic neuritis.[11-14] Our 5-year rate of 30% is lower than the previously reported rates, probably related to our having an incident cohort and a higher rate of patient retention, as well as possible differences in the criteria used to classify a patient as having CDMS.

Our finding that brain MRI is a powerful predictor of the short-term risk of MS is consistent with the findings of other studies.[15-21] In the study most comparable to ours, Morrissey et al.[19] reported the development of MS in 23 of 28 optic neuritis patients (82%) with an abnormal MRI scan and in one of 16 patients (6%) with a normal MRI scan within a mean follow-up of 5.5 years. We found a lower rate of MS in patients with an abnormal scan and a higher rate in patients with a normal scan. It is likely that the results of Morrissey et al.[19] are less precise due to a small sample size and are at least somewhat biased by the fact that follow-up was incomplete for one-third of their cohort due to patient withdrawals and losses to follow-up.

There is little consensus in the literature on the importance of prognostic factors other than brain MRI in predicting the development of MS after optic neuritis. Some studies have suggested that female gender and younger age are associated with a higher risk of MS while other studies have not.[11,12,22-25] We found a possible association of female gender with the development of CDMS only among those patients who had no brain MRI lesions. This is not surprising. Patients with abnormal brain MRI already have morphologic evidence of disseminated disease and as such it is expected that most of these patients will eventually develop additional neurologic events sufficient for a diagnosis of CDMS. Therefore all these patients could be considered to have MS at the time of optic neuritis, and thus there is no reason to expect to be able to identify true risk factors for future development of MS. On the other hand, the group of patients with optic neuritis and normal brain MRI likely includes a subset of those destined to have MS, and a subset of those who may have optic neuritis unassociated with MS. Among these patients, demographic factors known to be associated with MS in the general population, such as female gender and Caucasian race, might have prognostic value for the development of MS.

Our study disclosed certain clinical features of monofocal optic neuritis—lack of pain, presence of optic disk edema (particularly if severe or associated with hemorrhage or exudate), and presence of mild visual loss—which may have prognostic importance in projecting a low risk for development of MS. Bradley and Whitty[23] reported that the presence of pain, but not optic disk appearance or severity of visual loss, was associated with the development of MS. Kahana et al.[26] reported that MS was more likely to develop in optic neuritis patients with a normal disk (60% of 30 patients) than in those with a swollen disk (13% of 45 patients) within an average follow-up of 9.5 years.

Most of the patients in our cohort who developed CDMS had mild or no disability at 5 years. Whereas some studies have suggested that MS is more likely to follow a benign course when its first manifestation is in the optic nerve rather than in the brainstem or spinal cord,[27,28] other studies have concluded that the initial manifestation does not predict ultimate dis-

ability.[24] Our finding of an association between the number of brain MRI lesions and the degree of disability is consistent with that of Filippi et al.[20]

In a separate publication, we report the vision results after five years of follow up, including the risk of recurrent optic neuritis.[29] Recurrences of optic neuritis in either eye occurred in 28% of patients and were two-fold more frequent in patients who had or developed CDMS (46%) compared to patients without CDMS (22%). The comparatively higher recurrence rate in the prednisone treatment group that was reported previously[1,4] was predominantly present among the patients who did not have clinical or MRI evidence of MS.

With the support of the National Eye Institute, this cohort will continue to be followed. Reexamination of all patients is planned for 2001, marking 10 to 12 years of follow-up. Of special interest will be the status of the patients who have not yet developed MS, particularly those with normal brain MRI and clinical features suggesting a low risk for MS.

Acknowledgments

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Risk factors for developing multiple sclerosis after childhood optic neuritis

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Article abstract—We reviewed the records of all children (younger than 16 years of age) who presented with a diagnosis of optic neuritis (ON) identified through the comprehensive records-linkage system at the Mayo Clinic and identified 94 cases between 1950 and 1988 with a documented history of idiopathic ON. Detailed follow-up information was available on 79 patients, with a median length of follow-up of 19.4 years. Life-table analysis showed that 13% of the 79 patients with isolated ON had progressed to clinically or laboratory-supported definite multiple sclerosis (MS) by 10 years of follow-up, 19% by 20 years, 22% by 30 years, and 26% by 40 years. Gender, age, funduscopic findings, visual acuity, or family history of either ON or MS did not predict the development of MS. The presence of bilateral sequential or recurrent ON increased the risk of developing MS ($p = 0.002$; hazard ratio = 5.09), whereas the presence of infection within 2 weeks before the onset of ON decreased the risk of developing MS ($p = 0.060$; hazard ratio = 0.24). This study of childhood ON supports the lower risk of recurrence and progression to MS compared with adults.

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The genetic and environmental risk factors that predispose to the development of multiple sclerosis (MS) are incompletely understood. Of the potential risk factors identified to date, optic neuritis (ON) has been the most frequently associated with future development of MS.[1] Childhood ON appears to be different from the adult disease. Bilateral ON is more frequent in children[2-6] and is at times associated with systemic infections such as measles, mumps, chicken pox, pertussis, infectious mononucleosis, and immunizations.[4,5-11] A number of risk factors associated with an increased frequency of later MS after childhood ON have been suggested, including certain HLA antigens,[12,13] the presence of oligoclonal bands in the CSF,[4,12,13] female sex,[12] and unilateral disease.[5,12,14] Several retrospective and prospective studies have addressed the risk of developing MS after uncomplicated ON; however, these studies have either excluded children or included small numbers of children combined with a larger adult series.[4,5,12-22] The aims of this study were to determine important factors preceding the onset of ON in children

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