Optic Neuritis: Visual Outcome and Risk Factors for the Development of Multiple Sclerosis in Western Turkey

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ABSTRACT
Optic neuritis (ON) is highly associated with multiple sclerosis (MS) and conversion rate has been reported to be around 50% over a period of 15 years. We revised the risk factors for developing MS after an attack of ON, in western Turkey. One hundred and twenty-four patients with acute unilateral ON, who were on follow-up for at least 5 years (range 62 to 180 months, mean 85 months) were enrolled in the study. Gender, age at onset, seasonal occurrence, severity of visual loss, presence of pain, optic disc appearance, treatment, degree of recovery, presence or absence of lesions on magnetic resonance imaging (MRI) during the initial ON attack and recurrence were considered. Of the 124 patients, 89 (71.8%) were women, 35 (28.2%) were men, with a mean age of 28.7 ± 8.6 years at the time of the initial ON attack. During follow-up, 70 patients (56.5%) developed MS within 17.14 months, ranging from 1 to 125 months. Female gender (p = 0.021), experiencing the attack before 40 years of age (p = 0.02), normal-appearing optic discs (p = 0.005), presence of MRI lesions (p < 0.001), and recurring ON attacks (p = 0.014) were significantly associated with a high risk of developing MS. The period for development of MS was significantly shorter in patients with MRI lesions (p < 0.001). Optic neuritis patients with brain MRI findings showing the morphological evidence of disseminated disease can be considered to have MS at the time of the initial ON attack, and disease-modifying treatments can be initiated.

Keywords: magnetic resonance imaging, multiple sclerosis, optic neuritis

INTRODUCTION
Optic neuritis (ON) is an inflammatory, demyelinating condition that causes acute, usually monocular, visual loss. It is highly associated with multiple sclerosis (MS), occurring in 50% of the individuals at some time during the course of their illness.1–4 Risk of developing MS after ON has been reported to vary widely, ranging from 8% to 85%.5 In North America, the estimated cumulative 15-year probability of developing MS in patients with ON has been reported to be 50%.6 In the United Kingdom, 63% of patients with ON and other clinically isolated syndromes have developed MS over a period of 20 years.7 Subjects with bilateral, sequential, or recurrent ON, retrobulbar optic nerve involvement, neurological abnormalities outside the optic nerve, and an abnormal baseline brain magnetic resonance imaging (MRI) seem to have an increased risk.6,8 Other factors with impact on the risk for subsequent development of MS have been reported as female gender, young age, and winter season at onset of ON.6,10 Various studies have shown that more than 75% of ON patients with abnormal brain MRI develop MS within 15–20 years following the first episode of ON.4,11,12

The aim of the study was to revise the risk factors of developing MS after an attack of ON, in the western part of Turkey, in our outpatient cohort.

MATERIALS AND METHODS
The study enrolled 124 patients between the ages of 17 and 48 years, with acute unilateral ON, seen between January 1995 and January 2005. All the patients gave written informed consent prior to enrollment. The study was approved by the local Ethics Committee. Subjects were on follow-up for at least 5 years (range 62–180 months, mean 85 months). Standardized enhanced 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.

Diagnostic criteria for MS were based on the Poser clinical criteria for clinically definite MS (CDMS), up to 2001. Then, McDonald diagnostic criteria were used. To meet MS diagnostic criteria, a patient had to have a clinical examination documenting a second new neurological deficit attributable to central nervous system demyelination, consistent with neurological symptoms lasting at least 24 hours and separated by at least 4 weeks from the initial ON event. A second episode of ON in the same or the fellow eye was not regarded as dissemination in space or time and therefore not diagnostic of MS.

MS diagnosis date was the onset date of a second demyelinating event. For patients who did not develop MS, the last examination date was used as the censoring date for analysis.

Gender, age of onset (≤20, 21–39, ≥40 years), seasonal occurrence (spring, summer, autumn, winter), severity of visual loss, presence of pain, optic disc appearance, treatment with methylprednisolone, degree of recovery, MRI findings during the initial ON attack, and recurrence of ON attacks were taken into consideration. Visual acuity was graded into three degrees as follows: 1 = severe: visual acuity changing from absence of light perception to 3/10; 2 = moderate: visual acuity changing from 4/10 to 8/10; 3 = mild: visual acuity ≥9/10. Pain in or around the eye, preceding or occurring concurrently with visual loss, exacerbated by eye movement was accepted as presence of pain. ON attacks not associated with pain were regarded as painless. Optic disc appearance was recorded as normal or optic disc oedema. Patients receiving intravenous methylprednisolone for 3 days followed by oral prednisone (1 mg/kg/day) for 11 days according to the proposals of Optic Neuritis Treatment Trial (ONTT) constituted the treated group. Patients who were observed without treatment constituted the untreated group. Recovery of visual acuity was noted as complete if 9/10–10/10 was reached, partial if recovery of at least two lines was noted not reaching 9/10–10/10, or none if the improvement was at the level of one line or worse.

Three groups were defined according to the MRI findings during the initial ON attack: 1 = normal MRI; 2 = demyelinating lesions not meeting Barkhof’s criteria for MS; 3 = demyelinating lesions meeting Barkhof’s criteria for MS.

Statistical analysis was performed using SPSS for windows 17.0. Pearson chi-square test was used to compare the frequency of CDMS development according to gender, age at onset of ON, season at onset of ON, severity of visual loss, accompanying pain, optic disc appearance, treatment, recovery of ON, MRI findings, and recurrence of ON. Cumulative probabilities of development of CDMS were calculated with Kaplan-Meier estimates and statistically compared by the log-rank test.

RESULTS

Of the 124 patients studied, 89 (71.8%) were women, 35 (28.2%) were men, with a mean age of 28.7 ± 8.6 years at the time of the initial ON attack. During follow-up, 70 patients (56.5%) developed MS within 17.14 months, ranging from 1 month to 125 months. Factors predictive of development of CDMS in subjects with ON are given in Table 1.

Gender

Fifty-six (62.9%) of the 89 female patients developed CDMS. Fourteen (40%) of the 35 males developed CDMS. Female gender was significantly associated with high risk for CDMS development (p = 0.021).

Age at Onset

Twenty-one (16.9%) patients were ≤20 years of age during the initial ON attack, 9 (42.9%) of the subjects developed CDMS. There were 85 (68.5%) patients in the 21–39 years of age group, of whom 55 (64.7%) subjects developed CDMS. In 18 (14.5%) patients ≥40 years of age, 6 (33.3%) developed CDMS. Younger age at onset was significantly associated with high risk for development of CDMS (p = 0.02).

Season at Onset of ON

ON attacks were seen in spring, summer, autumn, and winter in 35, 30, 22, and 37 patients, respectively. The percent of development of CDMS in these groups were 60%, 53.3%, 59.1%, and 54.1%, respectively. No significant association was noted with the seasonal occurrence of the initial ON attack and CDMS development (p = 0.93).

Severity of Visual Loss

Visual loss was severe in 66 (53.2%) patients during the initial ON attack, 36 (54.5%) of whom developed MS. Forty-four (35.5%) patients were moderately affected, 27 (61.4%) of whom developed CDMS. Fourteen (11.3%) patients were mildly affected, seven (50%) of whom developed CDMS. The degree of visual loss was not significantly associated with development of CDMS (p = 0.68).
Accompanying Pain

One hundred (80.6%) of the 124 patients had accompanying pain. Fifty-five (55%) of them developed CDMS. In just 24 (19.4%) patients, ON attack was painless. Fifteen (62.5%) of them developed CDMS. Presence of pain was not significantly associated with CDMS development ($p = 0.33$).

Optic Disc Appearance

One hundred and one (81.5%) patients had normal-appearing optic discs, and 63 (62.4%) of them developed CDMS. In 23 (18.5%) patients optic discs were oedematous. Seven (30.4%) of them developed CDMS. Normal optic disc appearance was significantly associated with CDMS development ($p = 0.005$).

Treatment

One hundred and seven (86.3%) patients were treated with intravenous methylprednisolone, CDMS developed in 60 (56.1%) of them. Seventeen (13.7%) patients were followed up without treatment, CDMS developed in 10 (58.8%) of them. Treatment during the initial ON attack was not significantly associated with development of CDMS ($p = 0.524$).
Recovery from ON

Ninety-four (75.8%) of the 124 patients showed complete recovery. Twenty-eight (22.6%) patients showed partial recovery and two (1.6%) patients did not recover at all. Clinically definite multiple sclerosis development in the group showing complete recovery was 58.5% (55 patients) and 53.6% (15 patients) for the group showing partial recovery. Two patients without any recovery did not develop CDMS. Degree of recovery was not significantly associated with development of CDMS (p = 0.24).

MRI

Fifty-seven (46%) patients had normal MRIs. Ten (17.5%) of them developed CDMS. Nineteen (15.3%) patients had lesions not meeting Barkhof’s criteria for MS. CDMS development occurred in 17 (89.5%) of them. Forty-eight (38.7%) patients had MRIs compatible with MS. Development of CDMS was found in 43 (89.6%) of them. MRI findings during the initial ON attack were significantly associated with CDMS development (p < 0.001).

Recurrence of ON

Recurring ON attacks were noted in 26 (21%) patients, 20 (76.9%) of them developed CDMS. Of 98 (79%) patients with a single ON attack, 50 (51%) developed CDMS. Recurring attacks were significantly associated with high risk of developing CDMS (p = 0.014).

Fifty percent of women developed MS within 14 months (standard error [SE] = 0.06). For men this period was 18 months (SE = 0.1). No statistically significant difference was found between the two groups (p = 0.5). Other parameters taken into consideration did not show any statistically significant difference as well, when Kaplan-Meier survival analysis was performed. The only exception was the presence of MRI lesions. When the initial MRIs were normal, approximately 50% of patients developed CDMS within 48 months (SE = 0.15). On the other hand, CDMS developed within 14 months (SE = 0.12) if the subjects had MRI lesions not fulfilling Barkhof’s criteria and 8 months (SE = 0.07) if Barkhof’s criteria for MS were met (p < 0.001 for both groups, compared to normal MRI) (Figure 1).

DISCUSSION

The incidence of “observed” cases of multiple sclerosis developing after optic neuritis has been reported to range from 40% to 85% in previous studies. According to the follow-up studies of the ONTT, the risk of developing CDMS is 30% in 5 years and 50% in 15 years. In our study 56.5% of the subjects developed CDMS during a follow-up period of 5 years. Fifty percent of women developed MS within 14 months (SE = 0.06). For men this period was 18 months (SE = 0.1) and a statistically significant difference was not present between the two groups (p = 0.5). It has been noted in previous reports that most patients progressed to MS within 3 to 5 years. In our group the period was remarkably short.
Some clinical features associated with an initial ON attack have been reported as risk factors for CDMS development. However, there are several discrepancies amongst series. Young patients, those with winter onset and recurring ON attacks have been reported to be associated with a higher risk in two studies.\(^{10,20}\) On the other hand, Ghezzi et al.\(^{11}\) did not find gender, age, and season of ON onset as risk factors for developing CDMS. Male sex, lack of pain, optic disc swelling, and mild visual loss has been reported as low-risk factors in the 5- and 15-year follow-up studies of ONTT cohort.\(^{5,17}\)

In all those studies, presence of one or more MRI lesions has been reported to be highly associated with CDMS development.\(^{6,11,17,20}\)

In our study, female gender (\(p=0.021\)), ON attack taking place before 40 years of age (\(p=0.02\)), normal-appearing optic discs (\(p=0.005\)), presence of MRI lesions (\(p<0.001\)), and recurring ON attacks (\(p=0.014\)) were significantly associated with the development of CDMS.

Fifteen-year extension of the ONTT has found the risk of MS 3 times higher in women with normal baseline MRI, consistent with the well-described sex predilection of MS and MS was more than twice as likely to develop when ON affected the retrobulbar part of the optic nerve rather than the anterior optic nerve.\(^6\) Our data showing an increased risk in women and in patients with retrobulbar involvement are in accordance with the extension study. Young age at onset was significantly associated with CDMS development, as pointed out in previous studies.\(^{10,20}\)

Thirty-three percent of our patients over 39 years of age developed CDMS, whereas in the 21–39 years of age group this rate was 68.5%, indicating that younger patients have a 2-fold greater risk. Recurring ON attacks have been reported to be associated with a strong impact on the risk for subsequent development of MS.\(^{9,20}\) This was also the case in our patients. Development of CDMS was noted in 76.9% of our patients with recurring attacks and 51% of the patients with a single ON attack. The difference between the two groups was statistically significant (\(p=0.014\)).

Other parameters studied such as season at onset of ON (\(p=0.93\)), severity of visual loss during the initial event (\(p=0.68\)), accompanying pain (\(p=0.33\)), treatment with methylprednisolone (\(p=0.52\)), and recovery of vision (\(p=0.24\)) did not show a significant association.

Conflicting results are present about season at onset; some reporting a higher risk for patients affected in winter.\(^{10,20}\) Our result was concordant with the study of Ghezzi et al.\(^{11}\) not finding any association with season. Lack of pain and mild visual loss, which have been reported as low risk factors in the 5-year and 15-year extension studies of ONTT cohort, were not significantly associated with CDMS development in our patient group.\(^{6,17}\)

The presence of brain MRI abnormalities at the time of an ON attack is known to be a strong predictor of clinically definite multiple sclerosis development.\(^{6,11,12,17,19}\)

Our study revealed similar findings. CDMS development was noted in just 17.5% of our patients with normal MRI. However, very high rates were found in patients with MRI lesions either satisfying or not satisfying Barkhoff’s criteria for MS (89.5% and 89.6%, respectively).

Survival analyses revealed that if the initial MRIs were normal, 50% of patients developed CDMS within 48 months. The period was 14 months (\(p<0.001\)) for patients with MRI lesions not meeting Barkhoff’s criteria for MS and 8 months (\(p<0.001\)) for patients with MRI lesions meeting Barkhoff’s criteria for MS, indicating that these patients could be considered to have MS at the time of the ON episode with brain MRI findings showing morphologic evidence of disseminated disease.

In conclusion, female gender, younger age at onset, normal-appearing discs on examination, recurring ON attacks, and an abnormal baseline MRI were the risk factors for developing CDMS in our patients with an initial ON attack. The most significant of all was the baseline MRI. A very short period for development of CDMS in patients with MRI lesions, even those not satisfying Barkhoff’s criteria, was the most striking feature, making it necessary to consider disease-modifying treatments at the time of the initial ON episode in these cases.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES


