

Progression of Optic Neuritis to Multiple Sclerosis in the County of Split-Dalmatia, Croatia

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ABSTRACT

The aim of this study was to determine the incidence of monosymptomatic optic neuritis (MON) and progression of MON to multiple sclerosis (MS) from the Mediterranean region of southern Europe in the County of Split-Dalmatia, Croatia during the 11 years period from 1991 to 2001. This study was made retrospectively on the 87 cases (59 female, aged 25.9±11.3 and 28 male aged 29.9±9.2) of MON, which were treated at the Department of Ophthalmology and Department of Neurology, Split, University Hospital, from January 1991 to December 2001. In each case the diagnosis was confirmed by a chart review and cases were ascribed to the data of admittance at hospital. The annual incidence of MON was 1.9 per 100,000 (95% CI, 0.4–3.5). The incidence among males was 1.2 (95% CI, 0–2.9) cases / 100,000 per year and 2.5 (95% CI, 0.1–4.9) among females. A significant seasonal variations in the incidence of MON was not found ($\chi^2=6.81$, $p=0.08$). MS developed in 20 of 87 patients (22.9%) and median time was 25 (SE 8) months, (95% CI, 9–41) after the MON onset. After two years 12.6% of patients with MON developed MS, 20.6% after 5 years and 22.9% after 10 years. MS was slightly but not significantly more frequent in women than in men ($\chi^2=0.72$, $p=0.3$). In conclusion, the progression of MON to MS in the County of Split-Dalmatia, Croatia was at a relatively moderate frequency.

Key words: optic neuritis, multiple sclerosis, incidence, progression

Introduction

Monosymptomatic optic neuritis (MON) often refers to the acute disease of the optic nerve caused by any inflammatory optic neuropathy^{1–3}. It typically manifests as sudden monocular visual loss accompanied by eye pain in young adults, with women more commonly affected than men^{1–3}. MON may be associated with a variety of systemic autoimmune disorders, but the most common form is acute demyelinating MON best known for its association with multiple sclerosis (MS)^{1–5}. Alternatively, the episode of MON may turn out to be an isolated and self-limited monophasic syndrome which will not go on to MS. The new diagnostic criteria for MS proposed by the American academy of neurology has been published recently⁷. The rate of conversion to MS is not exactly determined and studies report rates from 11.5% to 85%, but averages around 60%^{4–6,8–12}. For MON brain magnetic resonance imaging (MRI) lesions, oligoclonal bands or intratectal IgG in cerebrospinal fluid (CSF) and female sex are at higher risk of development of MS, while no

brain MRI lesions and normal CSF has a low-risk profile^{7,10–14}. In the Optic Neuritis Treatment Trial (ONTT) the risk of MS within 10 years after the first episode of MON was 56% among patients with one or more characteristic white-matter lesions at baseline, as compared with 22% among patients with no lesions¹⁰.

Abnormal brain MRI or CSF consistent with MS has a positive predictive value for MS in the 80% to 90% range^{13,14}. A difference in the rate of conversion to MS is likely to be due to number factors: study design, criteria of patient selection, length of follow-up and method of survey.

MON is regarded as a good marker of MS risk. Long term observation showed that the majority of the MON patients progressed to clinically definite MS^{4,10–11}

The aim of this study was to determine the incidence of MON and investigate the progression of MON to MS in the County of Split-Dalmatia, the southern part of Croatia during a 11 year period from 1991 to 2001.

Materials and Methods

We retrospectively reviewed the charts of 87 patients (59 female, aged 25.9 ± 11.3 and 28 male aged 29.9 ± 9.2) who presented with MON. All patients were treated at the Department of Ophthalmology and Department of Neurology, Split, University Hospital, from January 1991 to December 2001. In every patient the diagnosis was confirmed by a chart review and patients were ascribed to the data of onset of symptoms rather than the data of admittance at hospital. The criteria for entry into the study included a diagnosis of acute optic neuritis with decreased and non-correctable visual acuity of eight days or less, age between 18 and 46 years, no history of optic neuritis or ophthalmoscopic signs of optic atrophy in the affected eye, visual field loss, impaired color vision and a relative afferent pupillary defect. Patients with identified causes of optic nerve neuropathy such as infections in adjacent regions, previous treatment with corticosteroids for optic neuritis in the other eye, systemic diseases, retinal or other intraocular pathology with symptoms mimicking those of MON were excluded. At study entry the patients underwent ocular examinations including visual acuity, color vision testing, visual field testing (with the Goldmann perimeter), visual evoked potentials and standardized neurologic examinations. At the time of MON onset the Poser criteria were used to exclude MS¹⁵. In brief, patients with clinically definite MS (CDMS) included two attacks and clinical evidence of two separate lesions (CDMS1) or two attacks and clinical evidence of one lesion and paraclinical evidence of another separate lesion (CDMS2); patients with laboratory – supported definitive (LSDMS) and patients with clinically probable MS (CPMS) were excluded. Treatment of MON mainly consisted of oral prednisone (1mg/kg), retrobulbar dexamethasone and since 1998 high-dose intravenous methylprednisolone. The high-dose intravenous methylprednisolone produce short-term reduction in the rate of development MS¹¹.

Detailed history and physical examination at baseline and follow period were performed. Follow-up neurologic and ocular examinations were performed after 3 months and 12 months and then yearly. The diagnosis of MS is based on longitudinal clinical and brain MRI acquired from the patients in the follow-up period. The characteristic demyelinating lesions were defined by its size (greater than or less than 3 mm), location (periventricular or nonperiventricular) and shape (ovoid or nonovoid). Patients were were instructed to report any new or worsening of preexisting symptoms.

Four patients were lost to clinical follow-up, having changed their address or refused further visit. The follow-up periods ranged from 64 to 132 months (mean 108 months). Disability was recorded with the Kurtzke expanded disability status scale (EDSS)¹⁶.

Population data for the County of Split-Dalmatia were based on the findings of the 2001 Croatia census and total population was 463,676¹⁷. Statistical analysis was performed using χ^2 test and descriptive statistics using

statistical package for computer (Statistica for Windows 6.0, StatSoft.Inc. Tulsa, USA). Confidence intervals (CIs) for incidence and relative risk (RR) were calculated at the level 95%¹⁸.

Time to diagnosis of MS was evaluated by the Kaplan-Meier method. The log-rank test was used to compare differences between the prognostic variables considered. Incidence rates were adjusted to the age and sex distribution using the European Standard Population¹⁹.

Results

During the 11-year period from 1991 through 2001, 87 cases of MON were diagnosed among residents in the County of Split-Dalmatia. 83 cases of MON were unilateral and 4 cases had bilateral involvement. 59 (67.8%) of the 87 patients were women and 28 (32.1%) men. The mean age at onset of MON was 25.9 years (SD 11.3) for females, and 29.9 years (SD 9.2) for males.

The annual incidence was 1.9 per 100,000 (95% CI, 0.4–3.5). The age and sex-specific incidence of MON is presented in Table 1. The incidence among males was 1.2 (95% CI, 0–2.9) cases / 100,000 per year and 2.5 (95% CI, 0.1–4.9) among females. The corresponding age-adjusted incidences were 1.3 per 100,000 person-years, 0.8 for male and 1.8 for females. Although the difference in incidence rates for women vs men was not significant, the relative risk (RR) for women was 1.4 (95% CI, 0.4–6.6). The peak incidence in both sexes observed in the group 20–29 years of age was 4.9 (95% CI, 0–11.4). RR of 20–29 years of age was 2.5 (95% CI, 1.4–4.3) compared with 0–19 years old group. Median visual acuity on the admission at hospital was 0.09 (range, 0.01–1.0). Median visual acuity 6 months after the attack of MON was 0.8 (range, 0.1–1.0).

A significant seasonal variations in the incidence of MON was not found ($\chi=6.81$, $p=0.08$). The seasons in this calculations were; spring (March, April, May), summer (June, July, August), autumn (September, October, November), winter (December, January, February). MS developed in 20 of 87 patients (22.9%) and median time to diagnosis of MS of entire MON population evaluated by the Kaplan-Meier method was 25 (SE 8) months, (95% CI, 9–41), Figure 1. After two years 12.6% of patients with MON developed MS, 20.6% after 5 years and 22.9%

TABLE 1
AGE AND SEX-SPECIFIC INCIDENCE OF OPTIC NEURITIS
AMONG COUNTY OF SPLIT-DALMATIA RESIDENTS, 1991
THROUGH 2001

Age Group, y	Men	Women	Total
0–19	0.4 (0–2.7)	3.7 (3.2–10.6)	2 (0–5.9)
20–29	3.3 (0–10.5)	6.8 (0–10.4)	4.9 (0–11.4)
30–39	3.1 (0–10.4)	2.6 (0–9.7)	2.8 (0–7.8)
> 40	0.3 (0–1.5)	0.7 (0–2.6)	0.5 (0–1.6)

* Values are given as incidence per 100,000 person per year (95% confidence interval).

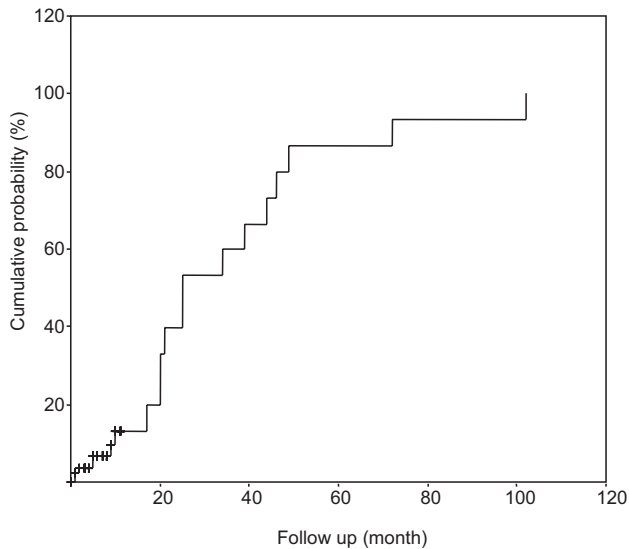


Fig. 1. Kaplan-Meier analysis of the cumulative probability of time to diagnosis of MS of entire MON population.

after 10 years. MS was slightly but not significantly more frequent in women than in men ($\chi^2=0.72$, $p=0.3$).

Discussion

A large number of studies have assessed the risk of development of MS after an isolated episode of MON^{4,6,8-12}. The variations in the risk of development of MS are mainly related to differences in criteria for diagnosis of MON and MS and in length of follow-up^{4,10-12}. The risk of MS steadily rises during the first 2 to 5 years following MON, but then increase more gradually. According to the review by Kurtzke, the risk ranges from 10% to 64% after 10 years³. In the ONTT the overall risk for development of MS after an initially isolated episode of MON was 30% at 5 year and 38% at 10-year follow-up^{10,11}. It is interesting to note that in our study although the MS was more frequent in women than men, a significant difference was not found. MS has been reported to be most likely to develop within the first 2 to 5 years following acute MON¹⁰⁻¹¹. The risk calculated in our study confirmed that MS usually occurs within the first 2-5 years with median time of 25 months to diagnosis of MS. The overall rate of progression of MON to MS in County of Split-

-Dalmatia after 5 and 10 years was generally lower than in other studies. Rodriguez et al. found the risk for MS was 39% after 10 years⁸. Kinnunen found by life time table analysis that the probability of developing MS after 9 years was 36%²⁰. In the study of Soderstorm et al. the calculation risk was 36% after 2.1 years and in the study of Ghezzi et al. the observed risk was 30% at 4 years²¹⁻²². The ONTT findings have shown that the proportion of patients who developed MS continued to increase with the length of follow-up¹⁰⁻¹². In the Optic Neuritis Study Group, the recurrences of MON were more frequent in patients with MS and most patients retained good vision¹². The most potent predictor of MS was the presence of white matter lesions on the baseline MRI scan of the brain¹⁰. The presence of such one lesion at least 3 mm in diameter more than double the 10- years risk of MS¹⁰. In our study at baseline the Poser criteria were used to exclude MS¹⁵ and therefore is likely that the risk of developing MS could have been higher in our patients, if brain MRI had been done at study enrollment.

In our study the highest incidence of MON was found in the 20-29 age group and male to female ratio was 1.6. Although in our study the difference in incidence rates for women vs men was not significant ($p=0.08$), the relative risk for women was 1.4. This may be explained with relatively small cases of MON in our study, and in statistically non-significant differences. In the County of Split-Dalmatia, there is no private hospital or places that take care of MON except this hospital. It is still possible that some cases may have been unregistered; some cases may have been recognized and treated in other hospital in Croatia.

The recent report from 10-year follow-up from the Optic Neuritis Study Group cohort provides valuable MS prognostic information²³. Most patients who develop MS following an initial MON will have a relatively benign course for at least 10 years²³.

In conclusion, although this study has been made retrospectively with a relatively small number of cases treated at the end of the observed period (1998-2001) with high-dose intravenous methylprednisolone and without brain MRI performed at the beginning of the study, it shows that progression of MON to MS in the County of Split-Dalmatia is relatively moderate.

REFERENCES

- BALCER LJ, N Engl J Med, 354 (2006) 1273. — 2. BOOMER JA, SIATKOWSKI RM, Semin Ophthalmol, 18 (2003) 174. — 3. KURTZKE JF, Arch Neurol, 42 (1985) 704. — 4. ARNOLD AC, Am J Ophthalmol, 139 (2005) 1108. — 5. EBERS GC, Arch Neurol, 42 (1985) 702. — 6. SANDBERG-WOLLHEIM MH, BYNKE S, CRONQUIST S, HOLTAS P, PLATZ S, RYDER LP, Ann Neurol, 27 (1990) 386. — 7. MILLER AE, COYLE PK, Clinical features of multiple sclerosis. In: MILLER AE (Ed), Continuum: Lifelong learning in neurology. Multiple sclerosis (Lippincott Williams & Wilkins, Philadelphia, 2004). — 8. RODRIGEZ M, SIVA A, CROOSS SA, O'BRIEN PC, KURLAND LT, Neurology, 45 (1995) 244. — 9. WIKSTROM J, POSER S, RITTER G, Acta Neurol Scandinav, 61 (1980) 178. — 10. Optic Neuritis Study Group, Arch Ophthalmol, 121 (2003) 944. — 11. Optic Neuritis Study Group, Neurology, 49 (1997) 1404. — 12. Optic Neuritis Study Group, Am J Ophthalmol, 137 (2004) 77. — 13. BREX PA, CICCARELLI O, O'RIORDAN JI, SAILER H, THOMSON AJ, MILLER DH, N Engl J Med, 346 (2002) 158. — 14. FILIPPI M, ROCCA MA, WIESMANN M, MENNEA S, CERCIGNANI M, YOURSEY TA, SORMANI MP, COMI G, Am J Neuroradiol, 20 (1999) 1931. — 15. POSER CM, PATY DW, SCHEINBERG L, MCDONALD WI, DAVIS FAEBERS GC, Ann Neurol, 13 (1983) 227. — 16. KURTZKE JF, Neurology, 33 (1983) 144. — 17. The census of population, household and dwellings 31th March 2001, [in Croatian], (Central Bureau of Statistics, Republic of Croatia).

atia, Zagreb, 2003). — 18. GARDNER MJ, ALTMAN DG, Calculating confidence intervals for proportions and their differences. In: GARDNER MJ, ALTMAN DG (Eds), *Statistics with Confidence Intervals and Statistical Guidelines* (BMJ, London, 1989). — 19. United Nations Population Division. *World population prospect: the 2002 revision population database*, Available from: <http://esa.un.org/unpp/index.asp?panel=2>, accessed:

December 5, 2003. — 20. KINNUNEN E, *Acta Neurol Scand*, 68 (1983) 371. — 21. SODERSTROM M, YA-PING J, HILLERT JLINK II, *Neurology*, 50 (1998) 708. — 22. GHEZZI A, MARTINELLI V, TORRI V, ZAFFAARONI M, RODEGHER M, COMI G, *J Neurol*, 246 (1999) 770. — 23. Optic Neuritis Study Group, *Arch Neurol*, 61 (2004) 1386.

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PROGRESIJA OPTIČKOG NEURITISA U MULTIPLU SKLEROZU U SPLITSKO-DALMATINSKOJ ŽUPANIJI, HRVATSKA

S A Ž E T A K

Cilj ovog ispitivanja je bio odrediti incidenciju monosimptomatskog optičkog neuritisa (MON) i njegovu progresiju u multiplu sklerozu (MS) u mediteranskom dijelu južne Europe, u Hrvatskoj, Županiji splitsko-dalmatinskoj, u 11 godišnjem razdoblju od 1991 do 2001. godine. Ovo retrospektivno ispitivanje je učinjeno kod 87 bolesnika (59 žena u dobi od $25,9 \pm 11,3$ god. i 28 muškarca u dobi od $29,9 \pm 9,2$ god.) liječenih od MON-a u Klinici za očne bolesti i Klinici za neurologiju, Kliničke Bolnice Split od siječnja 1991. do prosinca 2001. godine. Kod svakog bolesnika dijagnoza je potvrđena uvidom u povijesti bolesti, a bolesnici su razvstani po datumu prijema u bolnicu. Godišnja incidencija je bila 1.9 na 100.000 stanovnika (95% CI, 0,4–3,5). Incidencija među muškarcima je bila 1,2 (95% CI, 0–2,9) slučaja na 100,000 stanovnika na godinu i 2,5 (95% CI, 0,1–4,9) među ženama. Značajne sezonske razlike u incidenciji MON-a nisu nađene ($\chi^2=6,81$, $p=0,08$). MS se razvila u 20 od 87 bolesnika (22,9%) sa medianom vremena od 25 (SE 8) mjeseci, (95% CI, 9–41) od pojave MON-a. Tijekom prve dvije godine od nastanka MON-a, od MS-e je obolilo 12,6% bolesnika, 20,6% poslije pet godina i 22,9% poslije deset godina. MS je bila neznatno, ali ne i značajnije češća kod žena nego kod muškaraca ($\chi^2=0,72$, $p=0,3$). U zaključku, rizik od razvoja MS-e nakon MON-a u Hrvatskoj, u Županiji splitsko-dalmatinskoj, relativno je umjeren.