
II. Time and Space Patterns

Ya-Ping Jin, MD; Jesús de Pedro-Cuesta, MD, PhD; Mats Söderström, MD, PhD; Hans Link, MD, PhD

Objectives: To describe the time and space patterns of patients with monosymptomatic optic neuritis (MON) in Stockholm County, Sweden, and to explore the role of environmental factors in the etiology of MON and multiple sclerosis.


Setting: Census based on referrals from 1.68 million inhabitants of Stockholm County.

Patients: One hundred forty-seven new patients with MON were consecutively referred by ophthalmologists and neurologists from January 1, 1990, through December 31, 1995. A standardized questionnaire was used for data collection.

Main Outcome Measures: Evaluations consisted of annual incidence, statistical significance of temporal aggregation, Knox test, likelihood score test applied to the ratio of the highest to lowest seasonal proportion of registered events, and standardized morbidity ratio for municipalities.

Results: We observed a seasonal pattern of MON incidence, with the highest incidence (31%) in the spring and the lowest (17%) in the winter (ratio of highest to lowest seasonal proportion, 1.84; 95% confidence interval, 1.13-3.01; \( P = .007 \)). The seasonal monthly incidences were correlated with the average number of sunny hours and the temperature. The presence of positive immune activity markers (ie, mononuclear pleocytosis and oligoclonal IgG bands in the cerebrospinal fluid) seemed to be linked to the onset of MON in winter. No aggregation by time, space, or month of birth was detected.

Conclusions: Monosymptomatic optic neuritis in Stockholm County occurred at an uneven frequency across the seasons, with the highest incidence in spring and the lowest in winter. This seasonal pattern is compatible with that described in most previous reports. Environmental and probable infectious factors unevenly distributed by season may play a role in the etiology and early clinical course of MON.

Arch Neurol. 1999;56:975-980

The term optic neuritis (ON) can refer to any inflammatory optic neuropathy; however, it most frequently indicates an acute disease of the optic nerve attributed to focal inflammation associated with demyelination. In the absence of history and/or signs of multiple sclerosis (MS) and systemic disease, such as systemic lupus erythematosus or sarcoidosis, ON is referred to as monosymptomatic optic neuritis (MON). The frequent progression of MON to MS, the common appearance of ON during the course of MS, and the results of MS necropsies suggest that ON is one of the clinical manifestations of MS and that the etiology of ON is related to that of MS.

Seasonal variations may influence disease occurrence. If seasonal fluctuations affect the onset of MON and MS, this may imply that MON or some of the clinical manifestations of MS are related to either causative or protective environmental factors that are more prevalent or virulent during different seasons. A study of MON may be advantageous for several reasons. First, the insidious clinical progress in some patients with MS may make it difficult for them to accurately report the time of disease onset. This contrasts with MON symptoms, which are characterized by acute decrease in visual acuity and are often accompanied by eye pain; consequently, patients with MON usually seek medical advice early in the course of the disease and can accurately state the time of onset. Second, a short interval between the onset of MON and the time of diagnosis is the rule for most patients with MON, while a diagnosis of MS requires follow-up that may last several years.
an MON study may capture certain features of MS (eg, the relapsing-remitting phase or benign MS). Studies of seasonal factors potentially implicated in demyelination may be particularly beneficial.

We conducted a population-based, prospective study of patients with MON in Stockholm County (SC), Sweden. In prior reports, we described the incidence of MON by age, sex, ethnicity, birth cohort, and the prognosis for conversion to MS. The purpose of this article is to describe the time and space patterns of MON incidence in SC.

RESULTS

The annual crude, sex-specific, and age-adjusted MON incidence rates are listed in Table 1. The year-by-year variation of crude incidence was modest, with the lowest value at the beginning of the observation period and a peak in 1992. The incidence per 100 000 person-years during the study period was 2.28 for women (age-adjusted, 2.28), 0.59 for men (age-adjusted, 0.53), and 1.46 for both sexes (age-adjusted, 1.40).

In SC, the average monthly number of MON cases during the observed 72-month period was 2.04 (SD, 1.49). The highest incidence for both women and men during a 3-month period (n = 11) was observed in May through July and August through October of 1992 and March through May of 1993 (P = .99). When examined separately by sex, P = .70 for 11 women with new cases observed in March through May of 1993, and P = .53 for 5 men with new cases observed in June through August of 1992. No MON epidemics were detected during the study period.
The monthly and seasonal distributions of MON onset in SC are shown in Figure 1. For both women and men, the highest monthly incidences were observed in October (n = 19) and May (n = 18), and the lowest in January (n = 5), February (n = 6), and December (n = 6). A remarkable seasonal variation was noted, with the lowest incidence in winter and the highest in spring. This seasonal pattern was significant for spring vs winter, whether spring is defined as April through June (ratio of highest to lowest seasonal proportion of registered events, 1.84; 95% CI, 1.13-3.01; P = .007) or as March through May (ratio of highest to lowest seasonal proportion of registered events, 2.76; 95% CI, 1.54-4.97; P < .001). A seasonal pattern was suggested, with the highest incidence in spring, a medium value in summer and autumn, and the lowest incidence in winter.

The distributions of personal and clinical characteristics in the 3 MON subgroups defined by onset of MON in different seasonal periods are shown in Table 2. No statistically significant variations were found among patients affected during the different onset periods. When groups A and C were compared, the patients with MON onset in winter (January-March) showed a trend toward increased proportions of pleocytosis in cerebrospinal fluid, oligoclonal bands in cerebrospinal fluid, and conversion to clinically definite MS during the study period. When groups B and C were compared, these differences were less impressive. When the analysis conducted after the spring season was redefined as March through May, the differences, except for pleocytosis, almost disappeared.

The distribution of month of birth for patients with MON and that of residents in Stockholm born during the same period (1935-1980) are depicted in Figure 2. Larger than expected numbers of births of patients with MON were seen in April, July, and September. However, no statistically significant difference was found between the observed and the expected monthly distribution (P = .19).

The MON incidence per 100 000 person-years for both sexes in the 25 municipalities ranged from 0 (Salem, Upplands-Bro, and Vaxholm) to 2.96 (Danderyd). The SMR ranged from 0 to 2.35 across these municipalities, exhibiting wide CIs (data not shown). No statistically significant geographical variation was found. The highest incidences of MON per 100 000 person-years were registered in Danderyd (2.96; 7 observed patients; SMR, 2.35) and Lidingo (2.60; 5 observed patients; SMR, 2.01), 2 neighboring municipalities located in the urban central SC region close to Stockholm, from which 65 patients were referred.

The relationship between the frequency of MON and different climatic variables is depicted in Figure 3. Positive, statistically significant associations were found for the average monthly number of sunny hours (r = 0.669, P = .02) and temperature (r = 0.635, P = .03).

The results of the study in SC show that MON occurred at an uneven frequency across seasons, with the highest incidence in spring and the lowest in winter. The higher occurrence of mononuclear pleocytosis and oligoclonal IgG bands in cerebrospinal fluid seemed to be linked to the onset of MON in winter. No aggregation by time, space, or month of birth was observed.

There has been considerable concern about the possible artificial nature of the reported MON seasonality caused by referral bias,20 vacation-influenced shifts in population, or the fact that patients were more willing to consider admission for apparently benign conditions during the winter than during the summer.12 In spite of the hard climatic conditions of winter in SC, we do not believe that such a bias exists in our results for several reasons. First, the time point we studied is the onset of MON, not the time when medical advice was sought. Second, patient access to specialists in SC is good. Third, the case findings were prospective and done on a population basis. Finally, the resident population in geographically isolated areas in SC is sparse. The quality of diagnosis in our study was considered to be high.11 Therefore, the seasonal variation that we describe here should not be artifactual, and the presence of seasonality for MON in SC may imply that seasonal environmental factors do play a role in the etiology of MON.

In a review of the literature, we found 10 articles in English with data regarding ON seasonal variations.2,12,20-27 The quality of these studies varied. Regard-

Table 1. Annual Crude and Age-Adjusted Incidence of MON per 100 000 Population in Stockholm County, Sweden, 1990-1995*

<table>
<thead>
<tr>
<th>Year</th>
<th>Women</th>
<th>Men</th>
<th>Both</th>
<th>Women</th>
<th>Men</th>
<th>Both</th>
<th>Women</th>
<th>Men</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>15</td>
<td>5</td>
<td>20</td>
<td>1.77</td>
<td>0.25</td>
<td>1.04</td>
<td>1.80</td>
<td>0.22</td>
<td>0.94</td>
</tr>
<tr>
<td>1991</td>
<td>15</td>
<td>5</td>
<td>20</td>
<td>1.76</td>
<td>0.62</td>
<td>1.21</td>
<td>1.78</td>
<td>0.58</td>
<td>1.18</td>
</tr>
<tr>
<td>1992</td>
<td>27</td>
<td>8</td>
<td>35</td>
<td>3.14</td>
<td>0.99</td>
<td>2.10</td>
<td>3.18</td>
<td>0.87</td>
<td>2.02</td>
</tr>
<tr>
<td>1993</td>
<td>25</td>
<td>6</td>
<td>31</td>
<td>2.89</td>
<td>0.73</td>
<td>1.84</td>
<td>2.92</td>
<td>0.65</td>
<td>1.77</td>
</tr>
<tr>
<td>1994</td>
<td>17</td>
<td>4</td>
<td>21</td>
<td>1.94</td>
<td>0.48</td>
<td>1.23</td>
<td>1.97</td>
<td>0.43</td>
<td>1.21</td>
</tr>
<tr>
<td>1995</td>
<td>19</td>
<td>4</td>
<td>23</td>
<td>2.15</td>
<td>0.48</td>
<td>1.33</td>
<td>2.01</td>
<td>0.45</td>
<td>1.24</td>
</tr>
<tr>
<td>All</td>
<td>118</td>
<td>29</td>
<td>147</td>
<td>2.28</td>
<td>0.59</td>
<td>1.46</td>
<td>2.28</td>
<td>0.53</td>
<td>1.40</td>
</tr>
</tbody>
</table>

*MON indicates monosymptomatic optic neuritis.
the lowest in autumn. The most recent report from the Optic Neuritis Treatment Trial showed the highest incidence of monofocal optic neuritis in spring and autumn and the lowest in winter. Therefore, most published results are compatible with a worldwide seasonal variation of MON similar to that observed in our study. The highest rates occurred in spring2,20-22,24,25,27 and the lowest occurred in autumn2,24 or winter,20,21,25 despite the considerable heterogeneity of these studies regarding (1) the completeness and details of diagnostic criteria,20,21,23,24 the period of case-finding,20,25 and the definition of seasonal time intervals23,24; (2) the inclusion of MON2,12,22,25-27 RN,21,23 or RN criteria after excluding MS20 or disregarding the presence of MS24; (3) the bases of study (either hospital-based12,20,23,25 or population-based2); (4) the sources of diagnosis identified by neurologic25 or ophthalmologic12,23,25 specialists or both2,24; (5) the measures of seasonal variability24; and (6) the assessment of statistical significance.2,12,23,25,26

The relationship between seasonal MON risk reported worldwide and climatic changes was not addressed in prior studies. We obtained information on monthly proportions of new ON/RN cases or recorded attacks and on climatic data for selected studies2,20-22,24 and reports.28-30 Associations (not shown) similar to those seen in SC were perceived in each study. When the data for 48 place- and month-specific categories were pooled and correlated, the corresponding coefficients for average temperature, number of sunny hours, and precipitation were 0.332 (P = .02), 0.296 (P = .04), and 0.153 (P = .30), respectively.

An etiologic interpretation of the seasonal variations of MON in SC, which may reflect a worldwide trend, is particularly tantalizing because SC provided a particularly favorable domain for such a study owing to the considerable seasonal variations of sunlight and because the opposite correlation has been reported for MS risk or prevalence.31,32 Multiple agents that are particularly infectious

Table 2. Characteristics of Monosymptomatic Optic Neuritis Subgrouped by Seasonality

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>A (Apr-Dec)</th>
<th>B (Apr-June)</th>
<th>C (Jan-Mar)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subgroup by Period of Onset, No. (%)‡†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>98/122 (80)</td>
<td>39/46 (85)</td>
<td>20/25 (80)</td>
<td>.99‡</td>
</tr>
<tr>
<td>Age at onset ≥40 y</td>
<td>37/122 (30)</td>
<td>14/46 (30)</td>
<td>5/25 (20)</td>
<td>.34</td>
</tr>
<tr>
<td>Dw2 phenotype</td>
<td>56/121 (46)</td>
<td>23/46 (50)</td>
<td>12/25 (48)</td>
<td>.87</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor visual acuity at onset</td>
<td>28/120 (23)</td>
<td>9/45 (20)</td>
<td>5/24 (21)</td>
<td>.79</td>
</tr>
<tr>
<td>Papillitis at onset</td>
<td>24/120 (20)</td>
<td>9/45 (20)</td>
<td>5/24 (21)</td>
<td>.89‡</td>
</tr>
<tr>
<td>Pleocytosis in CSF at onset</td>
<td>53/118 (45)</td>
<td>23/44 (53)</td>
<td>14/25 (56)</td>
<td>.77</td>
</tr>
<tr>
<td>High CSF IgG index (≥0.7)</td>
<td>65/118 (55)</td>
<td>24/44 (55)</td>
<td>13/25 (52)</td>
<td>.84</td>
</tr>
<tr>
<td>Oligoclonal bands in CSF</td>
<td>83/118 (65)</td>
<td>32/44 (73)</td>
<td>20/25 (80)</td>
<td>.50</td>
</tr>
<tr>
<td>3 or more MS-like lesions on MRI</td>
<td>53/95 (55)</td>
<td>21/39 (54)</td>
<td>11/20 (55)</td>
<td>.93</td>
</tr>
<tr>
<td>Visual acuity ≥0.5 at 6 mo after onset</td>
<td>117/120 (98)</td>
<td>44/45 (98)</td>
<td>23/24 (96)</td>
<td>.52‡</td>
</tr>
<tr>
<td>Conversion to clinically definite MS</td>
<td>40/122 (33)</td>
<td>15/46 (33)</td>
<td>13/25 (52)</td>
<td>.11</td>
</tr>
<tr>
<td>Duration of follow-up, d§</td>
<td>768 ± 593</td>
<td>824 ± 619</td>
<td>744 ± 588</td>
<td>.60</td>
</tr>
<tr>
<td>Disease duration until conversion to clinically definite MS, d§</td>
<td>396 ± 426</td>
<td>469 ± 495</td>
<td>382 ± 331</td>
<td>.59</td>
</tr>
</tbody>
</table>

*CSF indicates cerebrospinal fluid; MRI, magnetic resonance imaging; and MS, multiple sclerosis.
†Period A had high incidence, period B had the highest incidence, and period C had the lowest incidence.
‡Fisher exact text.
§Values are mean ± SD.

Figure 2. Distribution of monosymptomatic optic neuritis cases in Stockholm County, Sweden (1990-1995), by month of birth.
and potentially causally related to MS or MON may satisfy requirements of high prevalence in such environments or seasons. While seasonally varying respiratory viral infections have been identified as the most frequent event preceding relapses in patients with MS, and while demyelination is evident in both MON and MS relapses (suggesting that these 2 processes may be related), we propose that similar infectious phenomena, whether subclinical or not, underlie our findings and those of others for seasonal variation of MON and MS relapses.

If MON onset occurs in the winter, a higher proportion of cases with abnormal immune activity markers might correspond to a higher frequency of demyelination during the immediate, high-risk season, although this holds true only in short-term studies. The notion of month of birth; these 2 processes may be related, we propose that similar infectious phenomena, whether subclinical or not, underlie our findings and those of others for seasonal variation of MON and MS relapses.

If MON onset occurs in the winter, a higher proportion of cases with abnormal immune activity markers might correspond to a higher frequency of demyelination during the immediate, high-risk season, although this holds true only in short-term studies. The notion of month of birth; these 2 processes may be related, we propose that similar infectious phenomena, whether subclinical or not, underlie our findings and those of others for seasonal variation of MON and MS relapses.

If MON onset occurs in the winter, a higher proportion of cases with abnormal immune activity markers might correspond to a higher frequency of demyelination during the immediate, high-risk season, although this holds true only in short-term studies. The notion of month of birth; these 2 processes may be related, we propose that similar infectious phenomena, whether subclinical or not, underlie our findings and those of others for seasonal variation of MON and MS relapses.

If MON onset occurs in the winter, a higher proportion of cases with abnormal immune activity markers might correspond to a higher frequency of demyelination during the immediate, high-risk season, although this holds true only in short-term studies. The notion of month of birth; these 2 processes may be related, we propose that similar infectious phenomena, whether subclinical or not, underlie our findings and those of others for seasonal variation of MON and MS relapses.

In our study, the proportions of cases of MON that converted to MS during each of the first 3 years were systematically higher in the group with MON onset in January through March. The overall proportion converted for cases with onset during this period was 13 (52%) of 25 vs 36 (30%) of 122 for those with MON onset in April through December (P = .03). While the above appears to be consistent with the highest environmentally determined risk of new demyelination during the early course of winter-onset MON and similar long-term severity, our observation should be cautiously interpreted.

We are not aware of reports on the months of birth for patients with MON. The months of birth for patients with MS were different than those of the general population and occurred mainly in March through June in Denmark in a large-scale study of more than 6000 patients with MS. In a study of 2229 patients with MS in British Columbia, Sadovnick and Yee showed a similar association of month of birth; these findings were considered to be statistically significant by James upon reexamination. A recent, but not controlled, study on subjects with MS in Budapest, Hungary, showed a considerable number of births occurring in April and October. The modestly greater number of births in February, April, July, and September in our study population is difficult to interpret, since it may be a result of the small sample size.

The fact that 2 neighboring municipalities with the highest incidence of MON were also the municipalities with the highest income in SC is in accordance with the finding from Germany that education is linked to risk of MON. However, ascertainment, geography, or random variation may explain this pattern.

To conclude, we report a seasonal pattern of MON, with the highest incidence in spring and the lowest incidence in winter; our findings are well correlated with sunlight and temperature, which may have an impact early in the course of the disease.

Accepted for publication November 19, 1998.

This study was supported by grants from the Swedish Medical Association, the Swedish Multiple Sclerosis Society (NHR), and project 12230 of the Swedish Medical Research Council, Stockholm, Sweden; and by funds from the Karolinska Institute, Stockholm, and the Carlos III Institute of Health, Madrid, Spain.

We thank the ophthalmologists and neurologists in Stockholm County for referring their patients with optic neuritis for evaluation.

Corresponding author: Ya-Ping Jin, MD, Division of Neurology, R54, Karolinska Institute, Huddinge University Hospital, S-141 86, Huddinge, Sweden (e-mail: Ya-Ping.Jin@cnst.ki.se).

REFERENCES