
II. Time and Space Patterns

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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.

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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, and the common appearance of ON during the course of MS, 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. Third,


PATIENTS AND METHODS

STUDY POPULATION AND DATA COLLECTION

Stockholm County is located at latitude 59° north, has a surface area of 6490 km², and is subdivided into 25 municipalities. As of December 31, 1995, the population of these municipalities ranged from 8215 (Vaxholm) to 711 119 (Stockholm). The resident population of SC was 1 725 756. All ophthalmologists and neurologists active in SC were invited to refer patients with newly diagnosed or suspected ON to the Karolinska Institute at Huddinge University Hospital, Huddinge, Sweden. An ophthalmologist trained in neurology (M.S.) interviewed the patients and performed complete ophthalmologic and neurologic examinations from January 1, 1990, through December 31, 1995. Each patient’s personal identification number, sex, address, ethnic origin, date of ON onset, results of clinical examination, and paraclinical test results were recorded using a standardized questionnaire. Monosymptomatic optic neuritis was diagnosed according to the clinical criteria of Perkin and Rose as “a condition causing a relatively rapid onset of visual failure, in which no evidence for a toxic, vascular, or compressive etiology can be discovered, and where local retinal lesions have been excluded.” Patients with other causes of optic nerve neuropathy and retinal or other intraocular pathologic conditions with symptoms mimicking those of ON were excluded. Patients were also excluded if their history or neurologic examinations revealed abnormalities fulfilling the criteria of Poser et al for clinically definite, clinically probable, or laboratory-supported definite MS. The study protocol was approved by the ethics committee of the Karolinska Institute at Huddinge University Hospital; informed consent was obtained from all patients. A detailed description of the survey methods has been published elsewhere.

TEMPORAL PATTERNS

Annual crude and age-adjusted incidences by sex were calculated. The European standard population was used as a reference. The age- and sex-specific annual population during the study period for each municipality was obtained from Statistics Sweden. For purposes of identification of possible small MON epidemics, temporal aggregation in our series was analyzed using the Knox test scanning approach over a 3-month period.

Seasonal variation was studied according to the date of onset of clinical manifestations of MON and the differentiation of 4 seasons per year; each season included 3 consecutive months (eg, spring was April through June). The statistical significance of seasonality was assessed by applying the likelihood score test to the ratio of highest to lowest seasonal proportion of registered events occurring in the study period.

To explore the association between putative seasonally changing etiologic factors and the personal and clinical characteristics of patients with MON, 3 MON subgroups (A, B, and C) were defined after the pattern of seasonal variation of MON incidence was examined by onset during seasonal periods with different risk (see the “Results” section for an explanation of our choice of seasonal intervals). The statistical significance of differences among the 3 MON subgroups was assessed using the χ² test or the Fisher exact test for proportions. For comparison of means, the t test was used.

The distribution by month of birth of the 147 patients with MON born from 1935 through 1980 was compared with that of 439 281 live births from the Stockholm municipality resident population during the same period. Data for the latter distribution were obtained from Statistics Sweden and were used for the expected distribution pattern. The statistical significance of differences between these 2 distributions was assessed using the χ² test.

SPATIAL PATTERNS

Taking the incidence of MON in SC during the study period as a reference, the standardized morbidity ratio (SMR) was used to describe the geographical variation of risk in the 25 municipalities. The 95% confidence intervals (CIs) of SMR were obtained by the exact limits method. The distribution by month of birth of the 147 patients with MON born from 1935 through 1980 was compared with that of 439 281 live births from the Stockholm municipality resident population during the same period.

ANCILLARY CLIMATIC DATA

Since climate variation can be a marker for seasonal change, we correlated information on average monthly temperature, number of sunny hours, and precipitation for the 72 consecutive study months in SC with the corresponding monthly proportion of MON cases.
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>2</td>
<td>17</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 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 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 artifactual nature of the reported MON seasonality caused by referral bias, 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. 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. 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. The quality of these studies varied. Regard-
ing quality of diagnosis, it would be difficult to interpret data from a 1958-1962 national survey in Italy, since the highest incidences of both retrolubral neuritis (RN) and papillitis were observed in a group whose age range was 51 to 60 years; 50% of the cases of RN and 45% of the cases of papillitis occurred in patients older than 50 years. From 3 articles published in the 1950s and 1960s and based on reviews of hospital records, the highest number of cases was seen in spring (April-June) and the lowest in winter, showing good agreement with our results. Wuthrich and Rieder from Switzerland reported that the highest incidence of RN in patients with a history of MS occurred in spring and 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 spring and autumn and the lowest occurred in autumn or winter, despite the considerable heterogeneity of these studies regarding (1) the completeness and details of diagnostic criteria; (2) the period of case-finding; (3) the bases of diagnosis identified by neurologic or ophthalmologic specialists or both; (4) the sources of diagnosis identified by neurologic or ophthalmologic specialists or both; (5) the measures of seasonal variability; and (6) the assessment of statistical significance.

The relationship between seasonal MON risk and monthly proportions of new ON/RN cases or recorded attacks and on climatic data for selected studies and reports. 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. Multiple agents that are particularly infectious

<p>| Table 2. Characteristics of Monosymptomatic Optic Neuritis Subgrouped by Seasonality* |
|---------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>A (Apr-Dec)</th>
<th>B (Apr-June)</th>
<th>C (Jan-Mar)</th>
<th>A × C</th>
<th>B × C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal</td>
<td></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>&gt; .99‡</td>
<td>.74‡</td>
</tr>
<tr>
<td>Age at onset &gt; 40 y</td>
<td>37/122 (30)</td>
<td>14/46 (30)</td>
<td>5/25 (20)</td>
<td>.30</td>
<td>.34</td>
</tr>
<tr>
<td>Div2 phenotype</td>
<td>56/121 (46)</td>
<td>22/46 (50)</td>
<td>12/25 (48)</td>
<td>.88</td>
<td>.87</td>
</tr>
<tr>
<td>Clinical</td>
<td></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>
<td>&gt; .99‡</td>
</tr>
<tr>
<td>Papillitis at onset</td>
<td>24/120 (20)</td>
<td>9/45 (20)</td>
<td>5/24 (21)</td>
<td>&gt; .99‡</td>
<td>&gt; .99‡</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>.31</td>
<td>.37</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>.78</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>.33</td>
<td>.50</td>
</tr>
<tr>
<td>3 or more MS-like lesions on MRI</td>
<td>53/96 (55)</td>
<td>21/39 (54)</td>
<td>11/20 (53)</td>
<td>&gt; .99</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>
<td>&gt; .99‡</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>.07</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>.85</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>.92</td>
<td>.59</td>
</tr>
</tbody>
</table>

* CSF indicates cerebrospinal fluid; MRI, magnetic resonance imaging; and MS, multiple sclerosis.
† Fisher exact test.
‡ Values are mean ± SD.

Figure 2. Distribution of monosymptomatic optic neuritis cases in Stockholm County, Sweden (1990-1995), by month of birth.
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 an MON variant in winter is supported by 2 previous reports from Lund, Sweden,26 and the United Kingdom25 that suggest that MON with onset in the winter seems to convert more frequently to MS than MON with onset during the other seasons; however, this was not confirmed either in Rochester, Minn,6 or in the United Kingdom study after the follow-up period was extended.3 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.36 In a study of 2229 patients with MS in British Columbia, Sadovnick and Yee37 showed a similar association of month of birth; these findings were considered to be statistically significant by James38 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.39 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 Germany40 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.

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REFERENCES