MULTIPLE SCLEROSIS IN NORTHERN IRELAND

A study of the date and place of birth of patients

By

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SUMMARY

1,418 multiple sclerosis cases, 1,238 of whom were born in Northern Ireland, were analysed. A detailed study was made of the 783 cases born in Northern Ireland from 1901 to 1925. These cases were studied in relation to all live births that occurred in the administrative areas of the province during the period. The results showed a constant *case-rate over the years studied, and a remarkable deficiency of cases born in the city of Belfast.

It was concluded that the risk of developing multiple sclerosis is not independent of the place of birth, but is independent of the year of birth of patients.

INTRODUCTION

Circumstantial evidence from varied sources (Schapira, Poskanzer and Miller, 1963; Acheson, 1965; Millar, 1966; Dean, 1967; Kurtzke, 1968) suggests that multiple sclerosis is acquired in early life, probably in infancy, although its clinical manifestations appear much later.

However, most of the previous studies of the geographical distribution of the disease have dealt with the location of patients following the onset of the disease. There appears to be only one reported study (Acheson and Bachrach, 1960) which has dealt exclusively with the place of birth of multiple sclerosis patients, and there is none which deals with the date and place of birth together. If multiple sclerosis has a long latent period running into decades, then in view of the mobility of population as well as the rapid environmental changes which are occurring, it becomes clear that the circumstances of a patient at or immediately before the onset of the clinical manifestations of the disease might have no relevance to the aetiological factors of the disease.

AIM OF THE PRESENT STUDY

The aim of the present study was to use ascertained multiple sclerosis cases born in Northern Ireland to investigate the following null hypotheses:

1. The risk of developing multiple sclerosis is independent of the year of birth.
2. The risk of developing multiple sclerosis is independent of the place of birth.

*Case rate is used here to represent the number of persons born in a particular year who were subsequently ascertained as multiple sclerosis cases per 1,000 live births during their year of birth.
POPULATION STUDIED

Northern Ireland is particularly suitable for such a study because it is a small administrative unit, and its compact and isolated geographical position reduces the number of extrinsic variables which have to be standardised in comparative studies. It is also easier with a population of the size of Northern Ireland (1,480,000) to carry out studies involving the whole population, than is possible in other parts of the United Kingdom. Multiple sclerosis cases have been ascertained from all over the province since 1948, mainly by Dr. R. S. Allison and Dr. J. H. D. Millar. The advantage of this in terms of uniformity of diagnosis is clear. A central register of all the ascertained cases (living or dead) has been compiled. On 1st October, 1968, there were 1,418 cases on this register. Most of these cases were ascertained through a countrywide prevalence survey (Allison and Millar, 1954). The rest have been ascertained since the survey, through consultant clinics, hospital records and post-mortem reports. In the absence of any specific diagnostic test it is impossible to estimate the degree of ascertainment represented by this register, but the structure and administrative arrangements of the National Health Service in Northern Ireland are such that using the combination of methods listed above, and the diagnostic criteria of Allison and Millar, 1954 (which were adopted by the World Federation of Neurologists for epidemiological studies – Allison, 1960) very few cases are likely to have been missed.

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**Figure 1. The Administrative Divisions of Northern Ireland**

The figures show the distribution of ascertained cases of multiple sclerosis born in each area (1901-1925). The figures in brackets are the expected, the others the observed.
Of the total 1,418 cases, 1,238 were born in Northern Ireland of whom 783 were born during the period 1901 to 1925. These 783 cases formed the study population. It was thought that since the mean age of onset of clinical symptoms was 31 years, many of those born after 1925 and destined to develop the disease, might not have developed the disease by the time the study was undertaken; on the other hand, it is very likely that many patients who were born before 1901 were dead by the time ascertainment began in 1948.

**METHOD**

All the 783 cases were assigned to their year and administrative area of birth and studied in relation to all registered live births that occurred in these areas during the appropriate years. Using this approach (a historical prospective study, Clark and Hopkins, 1967) it was possible to estimate individual chances of developing the disease among the 1901–1925 five-year cohorts in Northern Ireland.

**Table I**

*The number of persons born in Northern Ireland annually from 1901 to 1925 who subsequently developed multiple sclerosis and the corresponding rates per 1,000 registered live births.*

| Year of Birth | Multiple Sclerosis Cases | Rate 1,000 Live Births |
|---------------|--------------------------|------------------------|
|               | Male | Female | Total |                         |
| 1901          | 8    | 10     | 18    | .58                      |
| 1902          | 17   | 15     | 32    | 1.03                     |
| 1903          | 11   | 22     | 33    | 1.06                     |
| 1904          | 15   | 21     | 36    | 1.13                     |
| 1905          | 13   | 17     | 30    | 0.97                     |
| 1906          | 11   | 19     | 30    | 0.97                     |
| 1907          | 11   | 18     | 29    | 0.94                     |
| 1908          | 24   | 17     | 41    | 1.32                     |
| 1909          | 12   | 24     | 36    | 1.16                     |
| 1910          | 17   | 23     | 40    | 1.33                     |
| 1911          | 12   | 20     | 32    | 1.03                     |
| 1912          | 12   | 16     | 28    | 0.93                     |
| 1913          | 14   | 20     | 34    | 1.13                     |
| 1914          | 14   | 21     | 35    | 1.17                     |
| 1915          | 15   | 14     | 29    | 1.04                     |
| 1916          | 15   | 20     | 35    | 1.30                     |
| 1917          | 10   | 13     | 23    | 0.92                     |
| 1918          | 12   | 15     | 27    | 1.04                     |
| 1919          | 10   | 20     | 30    | 1.10                     |
| 1920          | 17   | 21     | 38    | 1.15                     |
| 1921          | 20   | 15     | 35    | 1.17                     |
| 1922          | 13   | 20     | 33    | 1.10                     |
| 1923          | 15   | 14     | 29    | 0.97                     |
| 1924          | 7    | 16     | 23    | 0.82                     |
| 1925          | 10   | 17     | 27    | 0.96                     |
| Total         | 335  | 448    | 783   | 1.06                     |
Administratively Northern Ireland comprised six counties—Antrim, Armagh, Down, Fermanagh, Londonderry, Tyrone and the two county boroughs of Belfast and Londonderry. (Fig. 1).

However, the vital statistics for county Londonderry for the period before 1922 also included those of Londonderry county borough. Therefore, for this study Londonderry county and county borough were combined. Belfast’s population for the period of study was about 387,000, which was about ten times that of the next largest town, Londonderry.

RESULTS

Year of Birth of Patients

Table I shows the number of ascertained multiple sclerosis cases born each year in Northern Ireland and the corresponding case rates per 1,000 live births. The average number was 31 and the case-rate of 1.1 per 1,000 was remarkably constant for the 25 years studied.

Table II shows the case rates for the administrative areas of Northern Ireland. Due to the small number of cases born yearly in each administrative area, the rates were calculated for quinquennial periods. Apart from one or two figures these rates are also practically constant for each area during the five quinquennia. It is, therefore, concluded, that there are no grounds for rejecting the null hypothesis that the risk of developing multiple sclerosis is independent of the year of birth of a patient.

Place of Birth of Patients

The overall case rates (for the period 1901–25) were Belfast 0.7, Londonderry 0.8, Antrim 1.2, Down 1.4, Armagh 1.4, Fermanagh 1.5, Tyrone 1.5. When Belfast’s rate was compared to the others using the approximation of standard error employed by the Registrar General (England and Wales) when comparing local death rates, significant differences were found in all instances except Londonderry—Table III. This exception of Londonderry may be due to the fact that Londonderry County Borough was studied with the Londonderry County as a single unit for reasons already given. Londonderry County Borough has about one-third of the total population of the two.

Table IV shows the comparison of the observed distribution of cases by administrative area of birth with the expected, based on the null hypothesis that all live births in Northern Ireland have an equal risk of developing multiple sclerosis. (The expected figures were calculated from the rate for the whole of Northern Ireland and the number of live births in each area during each quinquennium). The difference between the observed and the expected is highly significant ($X^2=124.8$, D.F.=34, $P<.001$). Again these figures show that fewer than expected cases were born in Belfast. The hypothesis that the risk of developing multiple sclerosis is independent of the place of birth is, therefore, rejected.

DISCUSSION AND CONCLUSIONS

In a previous study of the distribution of multiple sclerosis in Northern Ireland no significant differences were found in the distribution by administrative areas when the patients were studied by their addresses at the onset of the disease or at the time of ascertainment (Allison and Millar, 1954). The present study shows that a significantly smaller than expected number of cases were born in Belfast.
and a corresponding excess of cases were born in the other administrative areas of Northern Ireland. This finding was consistent over 25 years and could not be explained by any obvious bias in the material. It could not have been due to a greater availability of medical care, or to more accessibility of diagnostic facilities; on the contrary the deficiency of cases was in Belfast, which is the principal medical centre of Northern Ireland. Neither could it have been due to handicapped multiple sclerosis patients being left behind in the countryside while their more able-bodied contemporaries migrated to Belfast or abroad for work, because the analysis of cases was based on the date and place of birth, long before the patients developed their symptoms.

### TABLE II

**The number of persons born in the administrative areas of Northern Ireland from 1901 to 1025 who subsequently developed multiple sclerosis and the corresponding rates per 1,000 registered live births.**

*(Analysis for quinquennial periods)*

| Administrative Area | Overall Rate |
|---------------------|--------------|
|                     | 1901–05 | 1906–10 | 1911–15 | 1916–20 | 1921–25 | 1901–25 |
| Belfast             |         |         |         |         |         |         |
| County Borough      |         |         |         |         |         |         |
| Antrim County       |         |         |         |         |         |         |
| Armagh County       |         |         |         |         |         |         |
| Down County         |         |         |         |         |         |         |
| Fermanagh County    |         |         |         |         |         |         |
| Londonderry County & Co. Bor. | | | | | | |
| Tyrone County       |         |         |         |         |         |         |
| N. Ireland          |         |         |         |         |         |         |

1 = Number of cases.
2 = Live births 000s.
3 = Cases per 1,000 births.
This indicates that in Northern Ireland multiple sclerosis was due to a factor which operated less strongly in Belfast than in the other administrative areas of Northern Ireland during the first quarter of this century. Conversely, it could have been that a protective factor operated more strongly in Belfast.

It is concluded that the risk of developing multiple sclerosis in the population studied was independent of the year of birth, but was not independent of the place of birth.

The findings of this study provide only partial support to some of the aetiological factors which have been suggested in the literature.

1. Multiple sclerosis as an inherited disease:

   Evidence in favour:
   (i) The constant case rate of 1.1 per 1,000 live births in Northern Ireland during the years 1901 to 1925.
   (ii) From the only reported study of consanguineous marriages in the general population of Northern Ireland (Kilpatrick et al, 1955), areas of high cousin marriage rates correspond to the areas with high risk of developing multiple sclerosis.

### TABLE III

**Comparison of the overall case rate for Belfast with the case rates of the other administrative areas of Northern Ireland**

|              | $m_2 - m_1$ | $2 \sqrt{\frac{m_1^2 + m_2^2}{d_1 d_2}}$ | Comment   |
|--------------|-------------|------------------------------------------|-----------|
| ANTRIM       | 0.5         | 0.23                                     | Significant |
| ARMAGH       | 0.7         | 0.31                                     | "         |
| DOWN         | 0.7         | 0.25                                     | "         |
| FERMANAGH    | 0.8         | 0.44                                     | "         |
| LONDONDERRY  | 0.1         | 0.22                                     | Not Significant |
| (including county borough) |             |                                           |           |
| TYRONE       | 0.8         | 0.30                                     | Significant |

Where $m$ is the case rate and $d$ the number of ascertained cases $m_1$ and $d_1$ refer to Belfast and $m_2$ and $d_2$ to the other areas in Northern Ireland.
### Table IV

Comparison of the observed and expected distributions of multiple sclerosis cases born in the administrative areas of Northern Ireland on the null hypothesis that all live births had an equal risk of developing multiple sclerosis.

| Year of Birth | Belfast Co. Bo. | Co. Antrim | Co. Armagh | Co. Down | Co. Fermanagh (inc. Co. Bo.) | L'derry | Co. Tyrone | Total |
|---------------|----------------|------------|------------|----------|----------------------------|---------|------------|-------|
| 1901–05       | 42 (59.09)     | 25 (24.27) | 16 (14.77) | 34 (25.34) | 8 (7.39)                  | 9 (17.94) | 15 (15.83) | 149   |
| 1906–10       | 43 (59.09)     | 34 (24.27) | 17 (14.77) | 34 (24.27) | 8 (7.39)                  | 18 (17.94) | 22 (15.83) | 176   |
| 1911–15       | 35 (56.98)     | 31 (23.21) | 21 (13.72) | 35 (23.21) | 13 (6.33)                 | 8 (16.88) | 15 (15.83) | 158   |
| 1916–20       | 30 (53.82)     | 24 (21.10) | 16 (11.61) | 33 (21.10) | 10 (6.33)                 | 17 (15.83) | 23 (14.77) | 153   |
| 1921–25       | 35 (56.98)     | 19 (22.16) | 20 (12.66) | 14 (23.21) | 9 (6.33)                  | 16 (17.94) | 34 (14.77) | 147   |
| Total (observed) | 185           | 133        | 90         | 150       | 48                        | 68       | 109        | 783   |

**Overall rate** 1.055 cases/1,000 registered live births.  
D.F. = 34  
$X^2 = 124.8$  
P < 0.001 (highly significant)
Evidence against:
The evidence presented here in favour of a genetic basis of multiple sclerosis is indirect. The question can only be settled by the examination and analysis of all sibships of all the propositi, and the data required for such analysis was not available for this study.

2. Multiple sclerosis as a disease caused by an infectious agent, probably a virus:

Evidence in favour:
(i) Areas of high risk in Northern Ireland were found to coincide with areas of inadequate piped water supply and poor sanitation.

Evidence against:
(i) Year of birth of patients in Northern Ireland showed no epidemic pattern.
(ii) No seasonal incidence in the date of birth of patients was found (G. A. Ashitey, 1969).
(iii) No evidence of clustering of cases by date and place of birth together was obtained (G. A. Ashitey and G. MacKenzie, to be published).

Dean (1967) has suggested that multiple sclerosis is normally an infection of infancy, probably a gastrointestinal infection and those who escape because of high level of domestic hygiene may, if predisposed, develop the adult form of the disease. This hypothesis was based on Dean’s own findings in South Africa (1967), and the findings of other workers in different parts of the world (Alter et al, 1962; Westlund and Kurland, 1953; Okinaka et al, 1960).

It should be pointed out that all the above and other studies of multiple sclerosis have indicated so far is a higher prevalence of the disease in the developed western countries and a lower prevalence in the developing countries of Africa and Asia. There are many other differences between the above groups of countries besides domestic hygiene. Infant mortality rates (for which there are many causes) are widely different. Here it is interesting to note that from the data available (Registrar General, N.I., 1922) the infant mortality rate in Belfast (where fewer than expected cases were born) was higher than that in the other parts of Northern Ireland (where more cases of multiple sclerosis than expected were born); but it was also known that Belfast had a better sanitation and water supply than the rest of Northern Ireland (Adams and Cheeseman, 1951). What this “apparent” geographical distribution of multiple sclerosis therefore means in terms of aetiology is not clear, except perhaps in supporting the hypothesis that the “critical period” in the aetiology of multiple sclerosis is during infancy. The disease is less prevalent among people born in places of high infant mortality, and vice versa.

3. Multiple sclerosis and mineral deficiency or excess:

Evidence in favour:
(i) The constant case rate during the period 1901 to 1925.
(ii) One of the main differences between Belfast (low risk area) and the rest of Northern Ireland (high risk area) during 1901 to 1925 was in the water supply. Belfast had a piped water supply, while for most of the other parts of Northern Ireland the water used came from wells and streams. Stocks (1947), Morris et al (1961) and others have shown that local differences do exist in the mineral element composition of
drinking water, and that these can sometimes be correlated with the mortality and morbidity of certain diseases like cancer and cardiovascular diseases. Warren (1959) and others have suggested that a high prevalence of multiple sclerosis is associated with excess lead in the soil.

Evidence against:
Although Northern Ireland is known to have a varied geology within its small area, no chemical data have been obtained to show that the mineral composition of the water supply or the soil of the different administrative areas of the province are different.

4. Relationship between latitude and climate and multiple sclerosis:
Evidence in favour: Nil.
Evidence against:
There was a significant variation in risk of developing the disease between the administrative areas of Northern Ireland. The whole province lies within one degree latitude, and the climate is not very variable in the different areas of the province.

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