Age of Onset in Concordant Twins and Other Relative Pairs With Multiple Sclerosis

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Initially submitted October 17, 2008; accepted for publication April 24, 2009.

The ages of onset in multiple sclerosis cases span more than 7 decades. Data are presented for affected relative pairs from a Canadian population base of 30,000 multiple sclerosis index cases (1993–2008). The effects of genetic sharing, parent of origin, intergenerational versus collinear differences, and gender on the ages of onset were evaluated in the following concordant pairs: monozygotic twins (n = 29), dizygotic twins (n = 10), siblings (n = 614), first cousins (n = 405), half siblings (n = 29), parent/child (n = 285), and aunt/uncle/niece/nephew (avunculars) (n = 289). Fisher’s z test assessed intraclass correlation (r) for ages of onset. Correlations for monozygotic twins, dizygotic twins, full siblings, and first cousins were 0.60, 0.54, 0.20, and 0.10, respectively. Dizygotic twins resembled monozygotic twins more than siblings. The age-of-onset correlation for maternal half siblings (r = 0.37) was higher than that for paternal half siblings (r = 0.26), consistent with other observations suggesting an intrauterine environmental effect on multiple sclerosis risk. Intergenerational comparisons are complicated by substantial increases of multiple sclerosis incidence over time. Genetic loading (familial vs. sporadic cases) did not generally influence the age of onset, but correlation of age of onset in multiple sclerosis relative pairs was proportional to genetic sharing. A maternal parent-of-origin effect on the age of onset in collinear generations was suggested.

Abbreviations: CCPGSMS, Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis; SD, standard deviation.
influences. Prior studies had also suggested that the ages of onset for concordant monozygotic twins may be highly correlated (10, 13).

Here, we present age-of-onset data for a range of relative pairs concordant for multiple sclerosis. We selected several types of relative pairs for their potential to take into account the degree of genetic sharing, gender, and environmental exposures. Specifically, some categories of concordant pairs are differentiated by not only the degree of genetic sharing but also the exposure to the maternal uterine environment. Twins share the maternal uterine environment at the same time; full siblings and maternal half siblings share the same maternal uterine environment at different times, while paternal half siblings and first cousins have completely different maternal uterine environments. The age of onset has relevance for the timing of exposure to risk agents.

MATERIALS AND METHODS

Ethics approval

Ethics approval was obtained for all aspects of the Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis (CCPGSMS). The resources of the CCPGSMS have been previously described in numerous publications, including those by Orton et al. (9), Ramagopalan et al. (14), and Sadovnick et al. (15). As part of this nationwide, longitudinal, population-based protocol for data collection, age-of-onset information for index cases and their affected family members has been systematically obtained and validated. Both members of each affected pair had to be diagnosed according to new criteria for multiple sclerosis developed by Poser et al. (16) and/or the 2005 revisions to the “McDonald Criteria” described by Polman et al. (17).

Briefly for this study, between August 1993 and January 2008, multiple sclerosis clinics across Canada, with appropriate consent, used standardized telephone interviews to screen individuals with multiple sclerosis and to collect data about themselves and their families, including age of onset. All available clinical records were reviewed to confirm the information provided by the interviewees. If the affected relative was deceased, the age of onset was confirmed through available medical records obtained with appropriate next-of-kin consent.

Differences in mean ages of onset within an affected relative pair category

Differences in mean ages of onset within an affected relative pair category (e.g., siblings) were calculated as follows. The mean “earlier” age of onset was calculated by using cumulative data for each member of the concordant pair who reported his/her multiple sclerosis onset at the younger age (whether by months or years). The mean “later” age of onset for each group was calculated by using cumulative data for each member of the concordant pair who reported his/her onset at the older age (whether by months or years). The mean difference in ages of onset per category was then calculated by subtracting the earlier age of onset from the later age of onset. Comparisons for mean age of onset and mean difference in ages of onset were analyzed by a 1-tailed t test with Bonferroni’s method (18) to adjust for multiple tests.

Estimate of the strength of familial influences on age of onset

To study resemblance of ages of onset among N affected relative pair categories, we calculated the intraclass correlation coefficient ($r$). The 1-tailed $F$ test (19) was used to determine if the true value of $r$ was 0. If there was no aggregation of ages of onset within these pairs, $r = 0$. If the $F$ statistic was significantly larger than 1, then $r$ was significantly greater than 0, supporting intrapair resemblance for ages of onset.

Fisher’s $z$ test (19) was used here to test the equality of 2 intraclass correlation coefficients, $r_1$ and $r_2$. To do this, we first transformed each intraclass correlation coefficient as $r' = 0.5 \times \log_e (((1 + r)/(1 - r)))$. The test statistic is then computed as $z = (r_1' - r_2')/\sqrt{V}$, where $V = 1/(N_1 - 2) + 1/(N_2 - 2)$, and $N_i = \text{the number of concordant pairs in the $i$th group with} i = 1, 2$. Comparisons between $r_1$ and $r_2$ are done by using a 1-tailed $z$ test with adjustment for multiple comparisons (18). To do this, we equally divided the overall significance level at 0.05 among the $j$ tests of significance being contemplated. Thus, for each significance test in this study, the critical level of significance “alpha” = $0.05/j$, where $j$ is the number of tests. New alpha levels are given throughout the Results as appropriate.

RESULTS

For some of the relations discussed in this section, pairs were identified within the same family. Specifically, there were a total of 614 sibling pairs (517 distinct pairs; 97 pairs from 44 families), 29 half-sibling pairs (23 distinct pairs; 6 pairs—4 paternal, 2 maternal—from 3 families), 405 cousin pairs (320 distinct pairs; 85 pairs from 40 families), 285 parent/child pairs (260 distinct pairs; 25 pairs from 12 families), and 289 aunt/uncle/niece/nephew pairs (249 from distinct families; 40 from 17 families). The data were analyzed separately including and excluding the pairs from the same families (data not shown). Results did not differ (significant vs. not significant) when the data were reanalyzed by using only pairs from distinct families. Thus, all the available pairs were used in the results presented here.

Subjects

A search of the CCPGSMS database identified the following concordant affected relative pairs from collinear generations who were concordant for multiple sclerosis. All had validated information on age of onset and met the diagnostic criteria in use at the time of assessment and entry into the CCPGSMS database (16, 17):

1. Monozygotic twins ($n = 29$) (100% genetic sharing)
2. Dizygotic twins ($n = 10$) (50% genetic sharing)
3. Full siblings ($n = 614$) (50% genetic sharing)
4. Half siblings \((n = 29)\) (25% genetic sharing)
5. First cousins \((n = 405)\) (12.5% genetic sharing)

In addition, age-of-onset data were available for intergenerational affected relative pairs: 285 parent/child pairs (50% genetic sharing) and 289 avuncular (aunt/uncle/niece/nephew) pairs (25% genetic sharing).

### Mean ages of onset for sporadic and familial multiple sclerosis from the CCGPMS

By using the CCGPMS database, 12,284 individuals (8,794 females, 3,490 males) were identified who had no biologic relatives with multiple sclerosis, that is, sporadic cases. The overall mean age of onset for these cases was 32.41 (standard deviation \((SD) = 10.06\)) years: female mean age of onset, 31.96 \((SD = 9.97)\) years; male mean age of onset, 33.54 \((SD = 10.19)\) years. There were also 3,221 cases (2,311 females, 910 males) from 1,426 families having 2 or more family members (including the index case), that is, familial cases, diagnosed with multiple sclerosis according to criteria \((16, 17)\). The overall mean age of onset for these cases was 31.63 \((SD = 10.15)\) years: female mean age of onset, 31.53 \((SD = 10.16)\) years; male mean age of onset, 31.88 \((SD = 10.13)\) years.

Overall, the mean age of onset was older among sporadic cases compared with familial cases \((t = 3.909, df = 15,503, P = 4.7 \times 10^{-5})\), but in absolute terms, the difference was less than 1 year. Similarly, sporadic male cases had a significantly older mean age of onset compared with familial male cases \((t = 4.382, df = 4,398, P = 6.0 \times 10^{-6})\), but again, this difference was only about 1.5 years. Among females, sporadic cases showed a trend toward an older mean age of onset compared with familial cases by about half a year, but this did not reach significance \((t = 1.838, df = 1,838, P = 0.033)\). For the 3 tests done in this particular section, the adjusted significance level was 0.05/3 = 0.017.

### Median ages of onset

The median ages of onset for twins, sibling pairs, first-cousin pairs, and half-sibling pairs concordant for multiple sclerosis were 32 years, 30 years, 30 years, and 32 years, respectively. Table 1 gives the mean ages of onset for relative pairs from the same generation (collinear).

### Comparison of mean ages of onset in the same generation (collinear) relatives

**Children, nieces/nephews, first cousins.** The data are presented in Tables 1, 2, and 3. There was no difference in the mean age of onset for nieces/nephews of 28.33 years compared with children, where it was 27.65 years \((t = 0.98, df = 563, P = 0.16)\). However, compared with cousins who had a mean age of onset of 30.98 years, nieces/nephews \((t = 4.17, df = 1,043, P = 1.6 \times 10^{-5})\) and children \((t = 5.20, df = 1,048, P < 10^{-5})\) were both significantly younger at their mean ages of onset.

Nieces/nephews \((t = -3.50, df = 279, P = 2.7 \times 10^{-4})\) and children \((t = -4.67, df = 284, P = 2.0 \times 10^{-6})\) had significantly younger mean ages of onset compared with the general population’s mean age of onset of 30 years \((3)\), while the cousins \((t = 2.86, df = 764, P = 0.0022)\) had a slightly older mean age of onset. In addition, nieces/nephews \((t = 6.74, df = 12,562, P < 10^{-5})\), children \((t = 7.92, df = 12,567, P < 10^{-5})\), and cousins \((t = 3.83, df = 13,047, P = 6.5 \times 10^{-5})\) all had significantly younger mean ages of onset compared with the sporadic cases. For the 9 tests in this particular section, the adjusted significance level was 0.05/9 = 0.0056.

**Parents and aunts/uncles.** The mean age of onset for aunts/uncles was 36.97 years compared with 35.68 years for parents \((t = 1.29, df = 547, P = 0.099)\). However, for both these groups, the mean age of onset was older than that for the general population, with a mean of 30 years \((3)\): aunts/uncles \((t = 10.00, df = 274, P < 10^{-5})\) and parents \((t = 7.97, df = 273, P < 10^{-5})\). When compared with the mean age of onset for sporadic cases, the aunts/uncles \((t = 7.41, df = 12,557, P < 10^{-5})\) and parents \((t = 5.30, df = 12,556, P < 10^{-5})\) both had significantly older mean ages of onset.

| Table 1. Collinear Generations—Mean Age of Onset by Relationship and Gender, Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis, 1993–2008 |
|-------------------------------------------------------------|-------------|-------------------------------|
| Twin                                                        | Male/female | 36.33 (9.16)                  |
| All                                                         | 32.95 (8.10) |
| Male/female                                                 | 28.34 (8.52) |
| Female/female                                               | 30.60 (8.10) |
| Male/male                                                   | 31.35 (8.10) |
| All                                                         | 31.44 (8.10) |
| Sibling pair                                                | Male/female | 31.79 (9.99)                  |
| All                                                         | 31.28 (9.49) |
| Female/female                                               | 30.64 (8.87) |
| All                                                         | 30.71 (9.75) |
| Male/female                                                 | 30.73 (8.02) |
| All                                                         | 31.56 (9.58) |
| Cousin pair                                                 | Male/female | 31.66 (9.92)                  |
| All                                                         | 31.17 (9.85) |
| Female/female                                               | 29.81 (8.49) |
| All                                                         | 30.58 (7.94) |
| Male/female                                                 | 30.9 (8.28)  |
| All                                                         | 31.60 (10.58)|
| Male/male                                                   | 31.30 (8.50) |
| All                                                         | 31.52 (9.09) |
| Female/female                                               | 30.35 (7.44) |
| All                                                         | 31.60 (8.15) |
| Male/male                                                   | 30.72 (9.09) |
| All                                                         | 31.32 (9.92) |
| Female/female                                               | 30.73 (7.89) |
| All                                                         | 31.06 (9.85) |
| Male/female                                                 | 30.99 (8.94) |
| All                                                         | 30.70 (9.49) |
| Female/female                                               | 30.55 (7.44) |
| All                                                         | 30.79 (8.26) |
| Male/male                                                   | 31.28 (8.10) |
| All                                                         | 31.60 (9.75) |
| Male/male                                                   | 30.72 (9.09) |
| All                                                         | 30.71 (8.58) |
| Female/female                                               | 30.71 (9.09) |
| All                                                         | 30.35 (7.89) |
| Male/female                                                 | 31.32 (9.92) |
| All                                                         | 31.06 (9.85) |
| Female/female                                               | 30.73 (7.89) |
| All                                                         | 30.71 (8.58) |
| Male/male                                                   | 30.99 (8.94) |
| All                                                         | 30.70 (9.49) |
| Female/female                                               | 31.28 (8.10) |
| All                                                         | 31.60 (9.75) |
| Male/male                                                   | 31.32 (9.92) |
| All                                                         | 31.06 (9.85) |
| Male/male                                                   | 30.99 (8.94) |
| All                                                         | 30.70 (9.49) |

**Abbreviation: SD, standard deviation.**
Genetic sharing

Comparison of mean ages of onset for intragenerational concordant pairs

The mean age of onset for aunts/uncles was significantly older than that for nieces/nephews \((t = 10.26, \text{df} = 553, P < 10^{-5}\) as was the mean age of onset for parents compared with their children \((t = 9.26, \text{df} = 557, P < 10^{-5}\). For the 7 tests in this particular section, the adjusted significance level was 0.05/7 = 0.0071.

Genetic sharing

Tables 4 and 5 present data on differences in mean ages of onset and intraclass correlations \(r\). The data were subdivided by gender and the amount of genetic sharing. Overall, \(r\) decreased and the mean difference in age of onset increased with less genetic sharing. Concordant monozygotic twin pairs had a mean difference in age of onset of 7.62 years \((r = 0.54)\) as was the mean age of onset for parents, not significantly different \((t = 1.29, \text{df} = 27, P = 0.088)\). The difference predicted by the a priori hypothesis that the correlation would be higher for maternal versus paternal half siblings was found but did not reach statistical significance \((t = 1.39, \text{df} = 27, P = 0.088)\).

Generational differences

Data on ages of onset across generations are more difficult to evaluate compared with collinear generations because of various confounders including ascertainment, diagnostic issues, fecundity, and temporal changes in incidence/prevalence. A total of 285 parent/child pairs and 289 aunt/uncle/niece/nephew pairs were identified. The mean age at the time of the analyses presented here was 62.56 (SD = 10.18) years for parents, not significantly different from that for aunts and uncles (61.62 (SD = 11.07) years) \((t = 1.04, \text{df} = 547, P = 0.15)\) (Tables 7 and 8). The mean age of onset for parents was 35.68 (SD = 11.79) years compared with 36.97 years for aunts and uncles \((t = 1.29, \text{df} = 547, P = 0.099)\). Both of these mean ages of onset were older than those for children (27.65 years) and nieces/nephews (28.33 years) (Tables 7 and 8).
Table 4. Differences in Mean Ages of Onset by Gender and Genetic Sharing Among Concordant Pairs From Collinear Generations, Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis, 1993–2008

| No. of Pairs | Earlier Mean Age of Onset (SD), years | Later Mean Age of Onset (SD), years | Difference in Mean Ages of Onset (SD), years |
|--------------|--------------------------------------|-------------------------------------|---------------------------------------------|
| Twin         |                                      |                                     |                                             |
| Female/female| 30                                   | 28.40 (9.94)                        | 36.30 (10.86)                               |
| Male/female  | 3                                    | 32.67 (9.24)                        | 40.00 (9.17)                               |
| Male/male    | 6                                    | 26.50 (8.73)                        | 33.83 (8.01)                               |
| All          | 39                                   | 28.44 (9.59)                        | 36.21 (10.24)                              |
| Monozygotic twin |                                |                                     |                                             |
| Female/female| 25                                   | 28.32 (9.81)                        | 36.36 (10.89)                               |
| Male/male    | 4                                    | 26.75 (9.18)                        | 31.75 (9.46)                               |
| All          | 29                                   | 28.10 (9.58)                        | 35.72 (10.67)                              |
| Dizygotic twin |                                  |                                     |                                             |
| Female/female| 5                                    | 28.80 (11.78)                       | 36.00 (11.98)                               |
| Male/female  | 3                                    | 32.67 (9.24)                        | 40.00 (9.17)                               |
| Male/male    | 2                                    | 26.00 (11.31)                       | 38.00 (0.00)                               |
| All          | 10                                   | 29.40 (10.06)                       | 37.60 (9.26)                               |
| Sibling pair |                                      |                                     |                                             |
| Female/female| 313                                  | 26.44 (7.73)                        | 36.12 (8.59)                               |
| Male/female  | 250                                  | 26.79 (7.90)                        | 36.78 (9.35)                               |
| Male/male    | 51                                   | 26.73 (8.32)                        | 34.61 (10.26)                              |
| All          | 614                                  | 26.61 (7.84)                        | 36.27 (9.05)                               |
| Half-sibling pair |                               |                                     |                                             |
| Female/female| 13                                   | 25.08 (8.14)                        | 31.15 (7.48)                               |
| Male/female  | 14                                   | 28.07 (7.19)                        | 37.79 (7.54)                               |
| Male/male    | 2                                    | 34.00 (4.24)                        | 36.00 (2.83)                               |
| Maternal     | 19                                   | 27.42 (6.93)                        | 33.68 (6.72)                               |
| Paternal     | 10                                   | 26.60 (9.30)                        | 36.60 (9.72)                               |
| All          | 29                                   | 27.14 (7.67)                        | 34.69 (7.83)                               |
| Cousin pair  |                                      |                                     |                                             |
| Female/female| 204                                  | 25.85 (6.85)                        | 35.58 (8.44)                               |
| Male/female  | 149                                  | 25.98 (7.49)                        | 36.65 (9.17)                               |
| Male/male    | 52                                   | 25.56 (6.86)                        | 36.54 (9.34)                               |
| Maternal     | 217                                  | 25.42 (6.83)                        | 35.97 (8.82)                               |
| Paternal     | 188                                  | 26.37 (7.34)                        | 36.25 (8.84)                               |
| All          | 405                                  | 25.86 (7.08)                        | 36.10 (8.82)                               |

Abbreviation: SD, standard deviation.

The intraclass correlation coefficient for the paternal uncle-nephew pairs ($r = 0.65, n = 12, F = 4.64, P = 0.007, 95% confidence interval: 0.17, 0.88$) and the combined paternal uncle-niece/nephew pairs ($r = 0.25, n = 43, F = 1.68, P = 0.047, 95% confidence interval: −0.05, 0.51$) were nominally significant. However, after correction for multiple testing (14 tests for the maternal and paternal sides and 7 tests for the combined maternal/paternal sides), the adjusted significance level of 0.05 was 0.0024 made these results no longer significant. All the other intraclass correlation coefficients for different aunt/uncle/niece/nephew combinations did not differ from 0 (data not shown). All intraclass correlation coefficients for the different parent/child combinations did not differ from 0 (data not shown).

DISCUSSION

The age of onset in multiple sclerosis spans at least 7 or 8 decades, a distribution spanning an entire lifetime in Western countries (3). Overall, when concordant individuals are examined within a family, the degree of correlation in ages...
of onset has been modest, with sibling pairs showing more than a decade of difference in onset being not at all rare.

The results presented here are from the analysis of nearly 30,000 multiple sclerosis pedigrees from a population-based sample. We concede that the numbers for a few subgroups are small, but they are likely the best data available at present and for the immediate future.

There is considerable age specificity for multiple sclerosis onset with a peak at age 24 years and a mean age of 30 years in most series (3). The skewed distribution for fewer later-onset cases is manifest by there being less than 10% of cases beginning after age 50 (5, 6). When this happens, the primary progressive form of the disease is relatively over-represented (6, 20). The reason for this interesting distribution is not at all clear and pointedly does not follow the course seen in myasthenia gravis or rheumatoid arthritis. These 2 autoimmune diseases exhibit increasing incidence with age, especially in males (21, 22). Multiple sclerosis appears to follow a pattern consistent with the behavior of a susceptible population in whom there is a gradual waning of risk as those most susceptible cumulatively move from the general population pool of unaffected individuals to being diagnosed.

In theory, the association between genetic load and age of onset might be expected if early onset is a manifestation of greatest liability for a complex disorder (23). This pattern is not apparent here. There is a slightly older mean age of onset for the sporadic cases (approximately 1 year). These data suggest that early age of onset little reflects genetic load, consistent with there being no increase in affected relatives among pediatric cases (24).

Here, we have sought to explain the age distribution of multiple sclerosis by examining pairs of affected relatives from a population-based sample, which has been studied in much detail. Although not all comparisons cleanly distinguish between genes and environment, they do yield a number of observations. Overall, genes may be important determinants of age of onset as a relation between age-of-onset difference and degree of genetic sharing was seen. Simply put, affected pairs of relatives were more alike for

### Table 7. Mean Age at the Time of Analyses—Intergenerational, Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis, 1993–2008

| Parent-Child | No. | Mean Age (SD), years |
|--------------|-----|----------------------|
|              |     | Parent               | Child                |
| Mother-daughter | 164 | 61.84 (10.35)        | 37.77 (9.23)         |
| Mother-son    | 56  | 62.66 (8.87)         | 38.48 (8.64)         |
| Father-daughter | 45  | 64.31 (10.54)        | 40.84 (11.22)        |
| Father-son    | 20  | 65.65 (10.56)        | 37.85 (10.83)        |
| Mother-child  | 220 | 62.05 (9.98)         | 37.95 (9.07)         |
| Father-child  | 65  | 64.72 (10.48)        | 39.92 (11.11)        |
| Parent-child  | 285 | 62.65 (10.14)        | 38.40 (9.59)         |

Abbreviation: SD, standard deviation.

### Table 8. Mean Age at the Time of Analyses—Intergenerational, Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis, 1993–2008

| Aunt/Uncle/Niece/Nephew | No. | Mean Age (SD), years |
|-------------------------|-----|----------------------|
|                         |     | Aunt/Uncle           | Niece/Nephew        |
| Maternal side           |     |                      |                     |
| Aunt-niece              | 78  | 62.10 (11.35)        | 38.69 (9.42)        |
| Aunt-nephew             | 24  | 61.42 (7.82)         | 41.04 (8.52)        |
| Uncle-niece             | 26  | 63.27 (8.35)         | 39.50 (10.11)       |
| Uncle-nephew            | 17  | 61.82 (13.19)        | 39.24 (10.98)       |
| Aunt-niece/nephew       | 102 | 61.94 (10.59)        | 39.25 (9.23)        |
| Uncle-niece/nephew      | 43  | 62.70 (10.41)        | 39.40 (10.34)       |
| Aunt/uncle-niece/nephew | 145 | 62.17 (10.51)        | 39.29 (9.54)        |
| Paternal side           |     |                      |                     |
| Aunt-niece              | 73  | 60.25 (10.75)        | 37.97 (7.83)        |
| Aunt-nephew             | 28  | 61.86 (12.24)        | 40.11 (7.74)        |
| Uncle-niece             | 31  | 63.35 (10.72)        | 40.26 (10.11)       |
| Uncle-nephew            | 12  | 61.25 (16.61)        | 38.67 (13.82)       |
| Aunt-niece/nephew       | 101 | 60.69 (11.14)        | 38.56 (7.83)        |
| Uncle-niece/nephew      | 102 | 62.77 (12.46)        | 39.81 (11.11)       |
| Aunt/uncle-niece/nephew | 144 | 61.31 (11.55)        | 38.94 (8.91)        |
| Maternal and paternal sides | |                      |                     |
| Aunt-niece              | 151 | 61.21 (11.06)        | 38.34 (8.67)        |
| Aunt-nephew             | 52  | 61.65 (10.34)        | 40.54 (8.04)        |
| Uncle-niece             | 57  | 63.32 (9.63)         | 39.91 (10.03)       |
| Uncle-nephew            | 29  | 61.59 (14.42)        | 39.00 (12.00)       |
| Aunt-niece/nephew       | 203 | 61.32 (10.86)        | 38.91 (8.55)        |
| Uncle-niece/nephew      | 86  | 62.73 (11.41)        | 39.60 (10.67)       |
| Aunt/uncle-niece/nephew | 289 | 61.74 (11.03)        | 39.11 (9.22)        |

Abbreviation: SD, standard deviation.
ages of onset based on how close they were genetically, with the greatest degree of similarity seen for concordant monozygotic pairs \((r = 0.60)\) and the least for first-cousin pairs \((r = 0.10)\). However, because dizygotic and monozygotic twins had similar correlations in ages of onset, this genetic effect is neither simple nor straightforward.

Recently, but prior to the work presented here, intrauterine or early neonatal environment has been implicated in multiple sclerosis susceptibility. These data included a modest season of birth effect \((25)\), a maternal parent of origin effect in half siblings \((26)\) and avuncular pairs \((27)\), and a higher risk for dizygotic twins than for siblings within the same sibship \((13)\). These observations are extended here to an impact on age of onset. Dizygotic twins share the same number of genes as do siblings but show a much stronger age of onset correlation \((Table 5)\). Similarly, maternal half siblings are more strongly correlated than are paternal half siblings \((Table 5)\).

We also examined both collinear relative pairs (siblings, cousins, and half siblings) and intergenerational ones (aunt/uncle/niece/nephew, parent/child). These comparisons are complicated by the changes in prevalence/incidence of multiple sclerosis, well documented in Canada \((9)\) and elsewhere \((7, 8)\). Undoubtedly for ascertainment reasons, in parent/child and aunt/uncle/niece/nephew pairs, we found the mean ages of onset to be lower for the second generation (nieces/nephews; children) and for parents and aunts/uncles to have a significantly older mean age of onset compared with multiple sclerosis in general \((3)\) and sporadic multiple sclerosis from the CCPGMS.

The cohorts of aunts/uncles and parents are a generation older than the nieces/nephews and children who are at a higher risk of developing multiple sclerosis. This ensures that later-onset cases yet to develop are underrepresented in our sample of nieces/nephews and children. Nevertheless, there are several other factors that may influence intergenerational comparison. The clearest of these is the increasing incidence and prevalence of multiple sclerosis in Canada, which has resulted in a near tripling of multiple sclerosis over the last 3 generations based on alterations in the sex ratio, an effect largely limited to females \((9)\). This is evident within the aunt/uncle/niece/nephew population itself, manifested by the finding that affected nieces/nephews substantially outnumber aunts/uncles from the same families \((27)\). This effect is sufficiently large as to more than eliminate the anticipated countercurrent and substantial bias related to the age-specific onset of the disease \((27, 28)\). Here, there is a divergence between age of onset and susceptibility. Whereas for the latter it mattered who was the transmitting parent \((27)\), more likely to be the unaffected mother with an affected sib, no such effect was seen for age of onset.

In contrast to the data from the collinear relatives, which showed a relation of age of onset with both genetic sharing and parent of origin, intergenerational pairs of relatives with multiple sclerosis did not show any differences by gender of parent or offspring. These findings suggest that environmental risk factors are more likely to be temporally separate in these pairs.

The impact for recurrence risk counseling is modest but important to the individuals receiving this information. Historically, recurrence risk and remaining risk data were given on the basis of the wide age-of-onset ranges for the general population, and age adjustment was based on this as well \((28)\). The data presented here indicate that, depending on the genetic sharing and early environment, these risks can be refined considerably. For example, a female monozygotic co-twin of a multiple sclerosis patient has a risk of approximately 34% for the disease \((13)\). However, the data presented here on the mean difference in ages of onset between monozygotic female pairs suggest that very little of her risk would remain once she remained asymptomatic 8 years after her sister’s age of onset \((Table 4)\).

In summary, these data show that 1) the ages of onset in multiple sclerosis relative pairs are correlated, directly proportional to genetic sharing; and 2) a maternal parent-of-origin effect on the age of onset is suggested, which parallels that for susceptibility.

ACKNOWLEDGMENTS

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The Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis is funded by the Multiple Sclerosis Society of Canada Scientific Research Foundation. Dr. Reis’ sabbatical at the University of British Columbia was funded in part by Biogen Idec (France).

The authors thank Maria Criscuoli and Kevin Atkins for data collection and extraction. They acknowledge helpful discussions early in this project with Dr. Stefania Cannoni.

The following persons were members of the Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis Study Group: V. Devonshire, S. A. Hashimoto, J. Hooge, J. Oger, P. Smyth, P. Rieckmann, and J. T. Traboulsee (Vancouver); L. Metz (Calgary); S. Warren (Edmonton); W. Hader and K. Knox (Saskatoon); M. Freedman (Ottawa); D. Brunet (Kingston); J. Paulseth (Hamilton); G. Rice and M. Kremenutzky (London); P. O’Connor, T. Gray, and M. Hohol (Toronto); P. Duquette and Y. Lapiere (Montreal); T. J. Murray, V. Bhan, and C. Maxner (Halifax); and W. Pryse-Phillips and M. Stefanelli (St. Johns).

These data were presented in part at the XXth International Congress of Genetics, Berlin, Germany, July 12–17, 2008.

Conflict of interest: none declared.

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