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Original Contribution

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

A. Dessa Sadovnick, Irene M. Yee, Colleen Guimond, Jacques Reis, David A. Dyment, and George C. Ebers

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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.

age of onset; environment; family; genetics; multiple sclerosis; twins

Abbreviations: CCPGSMS, Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis; SD, standard deviation.

Multiple sclerosis, the most common neurologic disease of young adults, is characterized by myelin loss, various degrees of axonal pathology, and progressive neurologic dysfunction (1). The causes of multiple sclerosis are largely unknown, but it is clear that genetic and environmental components play important roles, both independently and interactively (2).

Most individuals have their clinical onset between the ages of 20 and 40 years. The peak age of onset is 24 years in females and 25 years in males (3). However, in large multiple sclerosis populations, the range of ages of onset is very broad to an extent matched by few disease entities. Well-documented pathologic cases are known early in the first decade of life (4) as well as into the ninth decade (5, 6). Explanations for this wide age-of-onset distribution are largely unknown. Environmental triggers for the precipitation of the clinical signs and symptoms have been vigorously sought. Specific triggers are infrequently identified, and evidence implicating triggering factors any more specific than viral infections in general has been hard to come by. Recent reports of increasing population rates of multiple sclerosis (7–9) now add another layer of complexity.

Some 2 decades ago, we reported a series of 99 sibling pairs concordant for multiple sclerosis found to have a greater age-of-onset correlation compared with randomly selected pairs of unrelated individuals (10). Similar findings based on 48 sibling pairs had been reported by Doolittle et al. (11). There also appears to be a modest but clear association of age of onset with the presence of the *HLA-DRB1*1501* allele (12), suggesting specific genetic

Correspondence to Dr. A. Dessa Sadovnick, Department of Medical Genetics, Vancouver Coastal Health Authority–University of British Columbia Hospital, G-920 Detwiller Pavilion, Vancouver, British Columbia V6T 2B5, Canada (e-mail: sadovnik@infinet.net).

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 = the number of concordant pairs in the ith 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 CCPGSMS

By using the CCPGSMS 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 ($t = 3.909$, 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

	No. of Pairs	No.	Mean Age of Onset (SD), years
Twin			
Female/female	30	60	32.35 (11.06)
Male/female	3	6	36.33 (9.16)
Male/male	6	12	30.17 (8.86)
All	39	78	32.32 (10.60)
Monozygotic twin	29	58	31.91 (10.76)
Dizygotic twin	10	20	33.50 (10.31)
Sibling pair			
Female/female	313	626	31.28 (9.49)
Male/female	250	500	31.79 (9.99)
Male/male	51	102	30.67 (10.10)
All	614	1,228	31.44 (9.75)
Half-sibling pair			
Female/female	13	26	28.12 (8.26)
Male/female	14	28	32.93 (8.76)
Male/male	2	4	35.00 (3.16)
All	29	58	30.91 (8.58)
Maternal	19	38	30.55 (7.44)
Paternal	10	20	31.60 (10.58)
Cousin pair			
Female/female	204	408	30.72 (9.09)
Male/female	149	298	31.32 (9.92)
Male/male	52	104	31.05 (9.85)
All	405	810	30.98 (9.49)
Maternal	217	434	30.70 (9.49)
Paternal	188	376	31.31 (9.50)

Abbreviation: SD, standard deviation.

Table 2. Intergenerational Pairs—Mean Age of Onset by Relationship and Gender, Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis, 1993–2008

Parent-Child Pairs	No. of Pairs	Mean Age of Onset (SD), years	
		Parent	Child
Mother-daughter	164	35.26 (12.16)	27.45 (7.76)
Mother-son	56	34.18 (10.65)	27.34 (7.42)
Father-daughter	45	36.38 (12.34)	29.44 (12.04)
Father-son	20	39.90 (10.87)	26.10 (7.50)
Mother-child	220	34.99 (11.78)	27.42 (7.66)
Father-child	65	37.46 (11.94)	28.42 (10.90)
Parent-child	285	35.55 (11.84)	27.65 (8.50)

Abbreviation: SD, standard deviation.

Table 3. Intergenerational Pairs—Mean Age of Onset by Relationship and Gender, Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis, 1993–2008

Aunt/Uncle/Niece/Nephew Pairs	No.	Mean Age of Onset (SD), years	
		Aunt/Uncle	Niece/Nephew
Maternal side			
Aunt-niece	78	37.86 (11.62)	27.67 (7.68)
Aunt-nephew	24	38.29 (10.29)	28.71 (8.79)
Uncle-niece	26	37.58 (10.27)	31.62 (9.64)
Uncle-nephew	17	38.76 (10.15)	26.12 (8.41)
Aunt-niece/nephew	102	37.96 (11.28)	27.91 (7.92)
Uncle-niece/nephew	43	38.05 (10.12)	29.44 (9.47)
Aunt/uncle-niece/nephew	145	37.99 (10.91)	28.37 (8.41)
Paternal side			
Aunt-niece	73	35.66 (13.03)	28.15 (6.71)
Aunt-nephew	28	39.64 (11.97)	29.07 (6.01)
Uncle-niece	31	36.26 (10.31)	27.74 (8.69)
Uncle-nephew	12	33.25 (10.79)	28.42 (10.09)
Aunt-niece/nephew	101	36.76 (12.81)	28.41 (6.51)
Uncle-niece/nephew	43	35.41 (10.41)	27.93 (8.98)
Aunt/uncle-niece/nephew	144	36.36 (12.13)	28.26 (7.30)
Maternal and paternal sides			
Aunt-niece	151	36.79 (12.33)	27.90 (7.21)
Aunt-nephew	52	39.02 (11.14)	28.90 (7.35)
Uncle-niece	57	36.86 (10.22)	29.51 (9.26)
Uncle-nephew	29	36.48 (10.60)	27.07 (9.04)
Aunt-niece/nephew	203	37.36 (12.05)	28.16 (7.24)
Uncle-niece/nephew	86	36.73 (10.29)	28.69 (9.21)
Aunt/uncle-niece/nephew	289	37.18 (11.54)	28.31 (7.86)

Abbreviation: SD, standard deviation.

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 ($t = 10.26$, df $= 553$, $P < 10^{-5}$) as was the mean age of onset for parents compared with their children ($t = 9.26$, 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 ($r = 0.60$) compared with 8.20 years for dizygotic pairs ($r = 0.54$), 9.66 years for sibling pairs ($r = 0.20$), and 10.24 ($r = 0.10$) years for first-cousin pairs.

Note that, because of the small sample size of dizygotic twins ($n = 10$), the 95% confidence interval included 0. As the r value for dizygotic pairs resembled that for monozygotic pairs more closely than that for sibling pairs, a decision was made to group monozygotic and dizygotic twin pairs for most comparisons.

The r value was significantly higher for twins compared with sib pairs ($z = 2.72$, $P = 0.0033$) and first-cousin pairs ($z = 3.27$, $P = 5.3 \times 10^{-4}$). All other comparisons (Table 6) were not significant. For the 11 tests conducted here, the adjusted significance level was $0.05/11 = 0.0045$.

Sharing of maternal environment

The impact of a common maternal uterine environment cannot be overlooked (refer to data for monozygotic vs. dizygotic twins and maternal vs. paternal half-sib pairs).

Maternal half siblings who shared the uterine environment of the same mother but at different points in time had a smaller mean difference in ages of onset (6.26 years) compared with paternal half siblings who shared the same number of genes but not the maternal environment (10.00 years) (Table 4). The small numbers (19 maternal half siblings; 10 paternal half siblings) resulted in large standard deviations. Thus, 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 ($t = 1.39$, 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) ($t = 1.04$, 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 ($t = 1.29$, 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.	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)	7.90 (6.21)
Male/female	3	32.67 (9.24)	40.00 (9.17)	7.33 (3.06)
Male/male	6	26.50 (8.73)	33.83 (8.01)	7.33 (6.44)
All	39	28.44 (9.59)	36.21 (10.24)	7.77 (5.95)
Monozygotic twin				
Female/female	25	28.32 (9.81)	36.36 (10.89)	8.04 (6.37)
Male/male	4	26.75 (9.18)	31.75 (9.46)	5.00 (2.16)
All	29	28.10 (9.58)	35.72 (10.67)	7.62 (6.03)
Dizygotic twin				
Female/female	5	28.80 (11.78)	36.00 (11.98)	7.20 (5.97)
Male/female	3	32.67 (9.24)	40.00 (9.17)	7.33 (3.06)
Male/male	2	26.00 (11.31)	38.00 (0.00)	12.00 (11.31)
All	10	29.40 (10.06)	37.60 (9.26)	8.20 (6.01)
Sibling pair				
Female/female	313	26.44 (7.73)	36.12 (8.59)	9.69 (7.49)
Female/male	250	26.79 (7.90)	36.78 (9.35)	9.99 (7.83)
Male/male	51	26.73 (8.32)	34.61 (10.26)	7.88 (8.16)
All	614	26.61 (7.84)	36.27 (9.05)	9.66 (7.69)
Half-sibling pair				
Female/female	13	25.08 (8.14)	31.15 (7.48)	6.08 (5.36)
Female/male	14	28.07 (7.19)	37.79 (7.54)	9.71 (8.17)
Male/male	2	34.00 (4.24)	36.00 (2.83)	2.00 (1.41)
Maternal	19	27.42 (6.93)	33.68 (6.72)	6.26 (5.74)
Paternal	10	26.60 (9.30)	36.60 (9.72)	10.00 (8.72)
All	29	27.14 (7.67)	34.69 (7.83)	7.55 (6.99)
Cousin pair				
Female/female	204	25.85 (6.85)	35.58 (8.44)	9.73 (7.17)
Female/male	149	25.98 (7.49)	36.65 (9.17)	10.67 (7.77)
Male/male	52	25.56 (6.86)	36.54 (9.34)	10.98 (8.27)
Maternal	217	25.42 (6.83)	35.97 (8.82)	10.54 (7.81)
Paternal	188	26.37 (7.34)	36.25 (8.84)	9.88 (7.21)
All	405	25.86 (7.08)	36.10 (8.82)	10.24 (7.54)

Abbreviation: SD, standard deviation.

Table 5. Intraclass Correlation for Ages of Onset Among Affected Relatives in Collinear Generations, by Relationship and Gender, Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis, 1993–2008

	No. of Pairs	Intraclass Correlation (r)	95% Confidence Interval	F	P Value
Monozygotic twins					
Female/female	25	0.58	0.25, 0.79	3.76	8.1×10^{-4}[a]
Male/male	4	0.85	0.09, 0.99	12.04	0.01800
All	29	0.60	0.31, 0.79	4.02	1.8×10^{-4}[a]
Dizygotic twins					
Female/female	5	0.74	−0.06, 0.97	6.58	0.032
Female/male	3	0.69	−0.49, 0.99	5.49	0.099
Male/male	2	−0.24	−0.97, 1.00	0.62	0.52
All	10	0.54	0.06, 0.86	3.39	0.035
Twin					
Female/female	30	0.60	0.31, 0.79	3.96	1.7×10^{-4}[a]
Female/male	3	0.69	−0.49, 0.99	5.49	0.099
Male/male	6	0.46	−0.38, 0.90	2.71	0.128
All	39	0.58	0.33, 0.76	3.78	3.6×10^{-5}[a]
Sibling pairs					
Female/female	313	0.17	0.06, 0.28	1.41	0.0013[a]
Female/male	250	0.19	0.07, 0.31	1.48	9.9×10^{-4}[a]
Male/male	51	0.38	0.12, 0.59	2.22	0.003
All	614	0.20	0.12, 0.27	1.49	$<10^{-5}$[a]
Half-sibling pairs					
Maternal half sibs	19	0.37	−0.078, 0.70	2.18	0.051
Paternal half sibs	10	0.26	−0.38, 0.74	1.70	0.211
All	29	0.30	−0.07, 0.59	1.84	0.055
First-cousin pairs					
Female/female	204	0.12	−0.02, 0.25	1.27	0.046
Female/male	149	0.12	−0.04, 0.27	1.27	0.077
Male/male	52	0.033	−0.24, 0.30	1.07	0.41
Maternal	217	0.044	−0.89, 0.18	1.09	0.26
Paternal	188	0.17	0.032, 0.31	1.42	0.008
All	405	0.10	0.007, 0.20	1.23	0.018

[a] There were 24 tests, and the alpha significance level was 0.05/24 = 0.0021.

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 0.05/21 = 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

Table 6. Results of Testing the Equality of 2 Intraclass Correlation Coefficients, Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis, 1993–2008

	z Score	*P* Value
Monozygotic versus dizygotic	0.22	0.41
Monozygotic versus sib pairs	2.49	0.0063
Dizygotic versus sib pairs	1.13	0.13
Monozygotic and dizygotic twins versus sib pairs	2.72	3.3×10^{-3}[a]
Monozygotic and dizygotic twins versus cousin pairs	3.27	5.3×10^{-4}[a]
Monozygotic and dizygotic twins versus half-sib pairs	1.39	0.082
Sib pairs versus cousin pairs	1.60	0.055
Sib pairs versus half-sib pairs	0.54	0.29
Sib pairs versus maternal half-sibs	0.76	0.23
Maternal half-sibs versus paternal half-sibs	0.29	0.39
Cousin pairs versus half-sib pairs	1.05	0.15

[a] There were 11 tests, and the significant alpha level was 0.05/11 = 0.0045.

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 overrepresented (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

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	43	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.

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

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 CCPGSMS.

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.

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Author affiliations: Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada (A. Dessa Sadovnick, Irene M. Yee, Colleen Guimond); Division of Neurology, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada (A. Dessa Sadovnick, Jacques Reis); the Wellcome Trust Center for Human Genetics, University of Oxford, Oxford, United Kingdom (George C. Ebers); and Department of Medical Genetics, University of Calgary, Calgary, Alberta, Canada (David A. Dyment).

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