Research letters

Parent-of-origin effect in multiple sclerosis: observations in half-siblings

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Multiple sclerosis is a complex trait in which occurrence rates in offspring are 20–50-fold greater than in the general population. Parent-of-origin effects have been difficult to screen for, since most cases are sporadic. We have compared recurrence risks in half-siblings with respect to their parent in common. Of the 1567 index cases with half-siblings in multiple sclerosis clinics across Canada, we recorded 3436 half-siblings and 2706 full-siblings. Age-adjusted full-sibling risk was 3·11%. By contrast, half-sibling risk in the same families was significantly lower at 1·89% (χ^2 test, p=0·006), but higher than expected if familial risk was simply polygenic. For maternal half-siblings, the risk was 2·35% (34 affected siblings of 1859), and 1·31% for paternal half-siblings (15 of 1577), (p=0·048). The difference in risk suggests a maternal parent-of-origin effect in multiple sclerosis susceptibility.

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Multiple sclerosis has characteristics of a complex trait. Susceptibility genes are implicated by an increased risk in monozygotic twins (20–30%) compared with dizygotic twins (3–5%).[1] A moderate excess of haplotype sharing in affected relative pairs[1] has accompanied multiple sclerosis associations with major histocompatibility antigens on a population level. Other genetic and environmental factors implicated by genetic epidemiology have remained elusive. With rising divorce rates, study of recurrence risks in half-siblings is a powerful method to test for parent-specific effects. We have reported[2] that in half-siblings of patients with multiple sclerosis, (1) no increased risk of the disease attributable to shared versus unshared familial environment was detectable, and (2) full-sibling occurrence risks exceeded those for half-siblings raised together. We have investigated recurrence risk within a family by looking at half-siblings and full-siblings of patients with multiple sclerosis.

Index cases (n=20 653) meeting criteria for clinically definite or probable multiple sclerosis and attending population-based regional multiple sclerosis clinics[3] across Canada were resurveyed. Relatives who were affected with multiple sclerosis were either examined, had their medical documentation reviewed, or both. Age-corrected risks were based on a modification of the maximum likelihood approach,[4] and comparisons between these risks were assessed with likelihood ratio tests. Crude risks were tested with the Davie's SE estimates.[5]

Of the 20 653 clinic cases screened by questionnaire, 1752 had at least one paternal or maternal half-sibling. Complete pedigree information was obtained for 1567 (89%) of these patients for analysis. Information was unavailable for the remaining 185 (11%), most often because the index case had died. Incomplete data were excluded before analysis. The 1567 index cases with complete pedigree information had a total of 3436 half-siblings and 2706 full-siblings, of known current age (or age at death) and known multiple sclerosis status. Of the 1567 patients, 726 had at least one maternal half-sibling, 610 had at least one paternal half-sibling, and 231 had at least one paternal and at least one maternal half-sibling.

49 half-siblings were affected with multiple sclerosis. Table 1 shows the crude risk and age-adjusted risk for half-siblings and full-siblings of the index cases. Age-adjusted risk for full-siblings was significantly higher than that for half-siblings (p=0·006).

Of the 1418 half-siblings who were raised with the index case, 20 had multiple sclerosis (age-adjusted risk 1·79% [95% CI 1·01–2·57]), whereas of 2018 half-siblings who did not share living environments, 29 had the disease (1·96% [1·25–2·67]). In most of those who had not shared accommodation, there had been no contact during childhood and often none in adulthood. The age-adjusted risks did not differ significantly. However, both half-sibling risks differed significantly from the full-sibling risk (for those raised together, p=0·0203; for those raised apart, p=0·0297). We saw no effect of common upbringing on risk in our data from adoptees.

Table 2 shows the crude risk and age-adjusted risk for maternal and paternal half-siblings of the index cases. The age-adjusted risks for maternal and paternal half-siblings differed significantly (p=0·048). Paternal half-siblings could have been under-represented, since non-paternity and paternal unfamiliarity would reduce the total number of half-siblings identified in a study of this type. Nevertheless, the number of paternal half-siblings identified was still 85% of maternal half-siblings.

We have shown that the half-sibling recurrence risk (1·89% overall and 1·79% for those raised together) was significantly lower than that for full-siblings living together (3·11%). This full-sibling rate mirrored that in (1) a population-based sample of 1044 multiple sclerosis patients in London, Ontario, Canada;[1] (2) full-siblings of twins;[1] and (3) the total population of Canadian multiple sclerosis patients in the Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis (Ebers GC, Sadovnick AD, unpublished data). In oligogenic or polygenic disorders, a steep drop in risk would be expected, because of the

	Number of siblings (with MS)	Crude risk (Davie's SE)	Age-adjusted recurrence risk	95% CI
Full-siblings	2706 (71)	2·62% (0·34)	3·11%	2·39–3·83%
Half-siblings	3436 (49)	1·43% (0·23)	1·89%	1·36–2·41%

MS=multiple sclerosis.

Table 1: **Age-adjusted risks for full-siblings and half-siblings of 1567 index cases**

	Number of half-siblings (with MS)	Crude risk (Davie's SE)	Age-adjusted risk	95% CI
Maternal half-siblings	1859 (34)	1·83% (0·36)	2·35%	1·57–3·13%
Paternal half-siblings	1577 (15)	0·95% (0·26)	1·31%	0·65–1·96%

MS=multiple sclerosis.

Table 2: **Age-adjusted risks for maternal and paternal half-siblings**

halving of the genes in common. However, our risk comparison does not conform to this expectation: the half-sibling rate was more than half the full-sibling rate. The non-significant excess of maternal half-sibling risk identified in our original study[3] suggested that parentally transmitted risk could be asymmetrical.

With the addition of new half-sibling families and the added follow-up of those surveyed in our original study, we show evidence for a significant maternal effect in multiple sclerosis occurrence, for which there are many potential explanations. Environmental factors might have a role in such an effect, and parental imprinting remains a possible candidate.

Our results entail important implications for the understanding of multiple sclerosis inheritance patterns and susceptibility. More generally applicable is the demonstration of the practicability, feasibility, and power of half-sibling data, which can answer basic questions about environmental sharing, pattern of inheritance, and the effect of parent of origin.

Contributors

G C Ebers and A Sadovnick were the principal investigators of the Canadian Collaborative Study. D Dyment, C Willer, and I Yee contributed to the analyses and manuscript preparation. N Risch provided discussion and statistical supervision.

Conflict of interest statement

None declared.

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