Maternal Transmission of Multiple Sclerosis in a Dutch Population

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Objective: To investigate the parental relationship of patients with multiple sclerosis (MS) from an extended pedigree with extensive genealogical information up to the middle of the 18th century.

Design: Multiple sclerosis is a complex disease resulting from genetic and environmental factors. Parent-of-origin effect, a phenomenon when the same allele may express differently depending on the sex of the transmitting parent, may influence the risk for MS. We investigated parental relationships between patients with MS using extensive genealogical information available from the Genetic Research in Isolated Populations program. We compared the average kinship of the parents of MS patients. We further explored the distribution of shortest genealogical links between parents of MS patients.

Subjects: Twenty-four MS patients from the isolated population who could be linked within a large complex pedigree, including 2471 people in total.

Results: The results consistently indicate a higher prevalence of maternal transmission of MS. The kinship between mothers of patients was 3.8 times higher than that between fathers (bootstrap \( P = .01 \)). Among the 814 shortest connections between parents, 333 were maternal (40.9%, vs 25.0% expected), 98 were paternal (12.0%, vs 25.0% expected), and 383 were maternal-paternal (47.1%, vs 50.0% expected) (\( P < .001 \)).

Conclusions: Mothers of MS patients were more closely related than their fathers. This skewed relationship shows evidence for a maternal effect in MS. The most likely explanation is a gene-environment effect that takes place in utero.

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Multiple sclerosis (MS) is a complex disease resulting from the interplay between genetic and environmental factors. Genetic factors are implicated to play a role in determining MS risk by adoption studies,\(^1\) studies with half-siblings,\(^2\) twin studies,\(^3\) and studies of conjugal MS.\(^4\) Migration studies\(^5,6\) have especially pointed to environmental factors as playing a role in MS.

Other influences, such as parent-of-origin effects, are also described in determining MS risk. Parent of origin is a phenomenon when the same allele is expressed differently depending on the sex of the transmitting parent. A study\(^2\) of half-siblings showed that maternal half-siblings have significantly higher risk of developing MS compared with paternal ones, suggesting a maternal parent-of-origin effect. In contrast, observations in offspring of affected parents demonstrated excess of paternal vs maternal transmission.\(^7\)

Both studies in which a parent-of-origin effect in MS was suggested were performed in differentially selected patient groups: with nonaffected parents in the study by Ebers et al\(^2\) and affected parents in the study by Kantarci et al.\(^7\) They had in common that only recent generations of patients with MS were studied.

We studied parent-of-origin effects of MS transmission in a genetically isolated population, with extensive genealogical information over centuries. Most cases were not closely related but were initially diagnosed as sporadic MS cases. The clinical MS phenotype was similar to MS in the general Dutch population.\(^8\)

Methods

**STUDY POPULATION AND PATIENT ASCERTAINMENT**

This study was performed within the framework of the previously described Genetic Research in Isolated Populations (GRIP) pro-
The Medical Ethics Committee of the Erasmus MC approved GRIP protocols. The GRIP population is a genetically isolated community in the southwest of the Netherlands. Fewer than 400 individuals founded the population in the middle of the 18th century. Considerable population growth subsequently occurred. Until recently, there was minimal immigration. An estimated 20,000 descendants of this population are scattered over 8 adjacent communities. The genealogical database contains information on more than 90,000 people, spanning 23 generations. Residents in the GRIP area are generally related via multiple lines of descent.

Ascertainment and clinical characteristics of MS patients in the GRIP population have been described in detail previously. In brief, 24 MS patients (5 men and 19 women) could be linked to the most recent common ancestor in 14 generations. These 24 MS patients had given written informed consent. Numerous connections exist between these patients via multiple common ancestors.

PARENT-OF-ORIGIN EFFECT

We compared average kinship of parents of the 24 MS patients, testing whether patients were more often related through paternal or maternal lineage. Kinship coefficients were computed using a computer software package (PEDIG). Under the null hypothesis of no parent-of-origin effect, the average degree of relationship of fathers should not be different from the one of mothers, assuming random mating.

When there is deviation from random mating (in particular, preferential outbreeding for one of the sexes), the test based on comparison of average kinships between mothers and fathers is not correct. For example, if there is systematic outbreeding of males, one would expect to observe higher kinship between mothers of any randomly selected group of people from the population.

To assess the empirical null distribution of differences in parental relationship specific for our population, we performed analysis using 10,000 replicates. For each time, 24 individuals, adjusted for sex and age with the patients, were randomly sampled from the GRIP genealogy database. This procedure is also known as bootstrap. Average kinship was computed for fathers and mothers of these randomly sampled individuals, and the ratio between maternal and paternal kinships was computed. The proportion of realizations in which the ratio was the observed ratio or more gives the empirical P value.

We further explored genealogical links between MS patients via all of their common ancestors using a software package (PEDIG). Under the null hypothesis of no parent-of-origin effect, the average degree of relationship of fathers should not be different from the one of mothers (0.0008). A 2-independent-samples test comparing these kinships gives a significant P value. Patients with MS could be linked to the most recent common ancestor in 14 generations ago. Finally, the mean (SD) kinship for the patients was 0.3.

To assess the parent-of-origin effect, we compared the mean kinship of mothers and the one of fathers. The mean kinship of mothers (0.0031) was 3.9 times higher than the one of fathers (0.0008). A 2-independent-samples test comparing these kinships gives a significant P value (<.0001). The empirical null distribution of the ratio between maternal and paternal kinships using 10,000 samples of 24 age- and sex-matched controls randomly selected from our genealogical database was derived. The probability of observing the same or a more extreme kinship ratio in this population was P = .01, indicating that closer kinship between mothers of MS patients is not a statistical artifact or a consequence of violation from the random mating assumption.

We further explored genealogical links between MS patients. In total, 36,466 pairwise connections between each possible pair of 24 MS patients were identified via

RESULTS

The general characteristics of the 24 MS patients are as follows. Their mean (SD) age at onset of symptoms was 29 (9) years; at diagnosis, 36 (11) years. There was no significant (P = .57) difference in age of symptom onset between the 24 MS patients and 73 sporadic Dutch MS patients from outside the isolate. There were 19 women (79%) in the sample. The distribution of relapse-onset MS (20 patients [83%]) and primary progressive onset MS (4 patients [17%]) was not different from that in the general MS population. Of the 24 patients, 15 were initially diagnosed as isolated MS cases and 9 were from families in which patients were themselves aware of having 2 or more MS cases in their families. Of these 9 patients, 4 were affected sisters from one family, all participating in this study. The other 5 patients were from families in which 2 people were diagnosed as having MS: 2 participate-}

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Among these connections, we counted shortest connections between each pair of MS patients in respect to the 3 possible patterns described in the “Methods” section. Among 814 shortest connections, 333 were between mothers (40.9%; 25.0% expected), 98 were between fathers (12.0%; 25.0% expected), and 383 were between a father and a mother (47.1%; 50.0% expected) ($P < .001$) (Figure).

We also investigated parent-of-origin effect for several other diseases in the GRIP area, using the same database and the same method. For 67 patients with Parkinson disease, 103 with late-onset Alzheimer disease ($P = .52$), and 39 with type 1 diabetes mellitus ($P = .38$) who could be linked to a common ancestor, no significant parent-of-origin effect could be found.

**Figure.** Observed distribution of connections between patients with multiple sclerosis (MS). Solid circles indicate female patients with MS; open circles, unaffected mothers of patients with MS; and open squares, unaffected fathers of patients with MS.

A pedigree of 24 patients with common clinical phenotypes of MS was recently reconstructed.8

Herein, we show that the shortest connection to a common ancestor between 2 individuals with MS was significantly more often through their nonaffected mother than through their nonaffected father, suggesting a maternal parent-of-origin effect. No significant parent-of-origin effect was observed in several other diseases in the same area. Thus, the effect seems to be specific for MS.

Mothers of the 24 MS patients were also more closely related to each other than their fathers.

Multiple sclerosis has a female-male ratio of 3:1. Potentially, this carries the risk of bias when studying disease transmission over 2 generations when parents are affected and women are at increased risk of MS. Our approach had no bias into this skew because none of the parents and grandparents of the 24 MS patients were affected with MS.8 A few other studies2,7,13 analyzed parent-of-origin effects, all using the information of 2 generations. The significant difference with our study is that by using extensive genealogical information we were able to study the shortest links by a multigenerational approach.

Our findings are in line with the results of the Canadian study in which the difference in MS risk was investigated for half-siblings of MS patients with a shared nonaffected parent. A shared mother was associated with a higher MS risk.2

In contrast, a recent study7 in the United States observed that fathers transmit the disease more frequently. This was explained by the Carter effect. According to this theory, men are more resistant to MS because they require a higher genetic load and thus are more likely to transmit the genetic risk of the disease to their children. This phenomenon was not observed by others.13 Our approach differed from that of Kantarci et al7 in that we did not study multiplex families and parents were not affected.

Taking together all available data on parental transmission of MS, one can conclude that the MS-affected status of the parent may influence transmission of disease.

Maternal transmission could be a result of several factors: genetic, environmental, or both. There are at least 3 single genetic explanations. None of them are supported heavily by current data. First, maternal effects could be exerted by direct transmission via mitochondrial genes or indirectly by autosomal genes involved in mitochondrial pathways, such as UCP2 (uncoupling protein 2 gene) (GenBank MIM 601 693). This gene has a neuroprotective function and may contribute to MS susceptibility.14,15 Thus far, attempts to link mitochondrial mutations with MS susceptibility have been disappointing.16-18

A second possible genetic explanation is genomic imprinting.19 This has been insufficiently explored.

A third explanation could be the interaction between genes and female-specific environmental factors, such as hormonal, intrauterine, or perinatal factors.

Recent findings have demonstrated an increasing female to male sex ratio, strongly suggesting an environmental origin. It seems that the relative role of environmental factors in determining MS susceptibility has changed during the past century, in possible interaction with genetic interactions.20

Our data show that MS patients are more often related through their mother than through their father, at least in the pedigree studied herein. Because MS in this pedigree has a common clinical phenotype and most cases were initially diagnosed as sporadic MS cases, our findings are likely to be representative of the total MS population. These findings support a maternal parent-of-origin effect in MS. There is reason to assume that this effect is caused by an interaction of genetic and environmental factors.21 Dense genotyping in this pedigree can help to unravel the genetic contribution, thus aiding in resolving the nature-nurture dilemma in MS.

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