Parent-of-origin effect in multiple sclerosis

Observations from interracial matings

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ABSTRACT

Background: Multiple sclerosis (MS) is a complex neurologic disease with a striking geographical distribution. In Canada, prevalence is high in Caucasians of Northern European ancestry and uncommon in North American Aboriginals, many of whom now have Caucasian admixture.

Methods: The population-based Canadian Collaborative Project on the Genetic Susceptibility to MS provided the characteristics of 58 individuals with 1 Caucasian and 1 North American Aboriginal parent from a database of 30,000 MS index cases.

Results: We found that MS index cases with a Caucasian mother and a North American Aboriginal father had a higher sib recurrence risk and greater F:M sex ratio ($p = 0.043$) than patients with a North American Aboriginal mother and Caucasian father.

Conclusions: Maternal parent-of-origin effects in multiple sclerosis disease etiology previously seen in studies of half-siblings and avuncular pairs are also seen in Caucasian-North American Aboriginal admixture matings and warrant further investigation. A differential influence of maternal risk transmission on the sex ratio of affected offspring is implied. The method of analysis used may have broader implications for detection of parent-of-origin effects in admixture cohorts. ***Neurology***® **2009;73:602–605**

GLOSSARY

CCPGSMS = Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis; **MS** = multiple sclerosis.

Multiple sclerosis (MS), an inflammatory disease of the CNS, is characterized by myelin loss, varying degrees of axonal pathology, and progressive neurologic dysfunction.[1] The causes of MS are largely unknown but an interplay of genetic and environmental components plays an important role.[1] In Canada, the prevalence of MS is approximately 240 per 100,000 among Caucasians of central and northern European origin[2]; figures are substantially lower for North American Aboriginals residing in the same regions.[3] A recent study identified 7 North American Aboriginal Canadians with MS in the province of Manitoba, yielding a prevalence of 40 per 100,000.[3] Of these 7, 6 reported 1 European ancestor each. Thus, the prevalence of MS in North American Aboriginals with no European ancestry remains uncertain, but can be assumed to be low.

The Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis (CCPGSMS) has collected information on a cohort of more than 30,000 families in which at least 1 member has MS, including data on the ethnic background of index cases, based at a minimum on the 4 grandparents. We used this large population-based sample to investigate MS occurrence in the offspring of 1 parent of Northern European ancestry and the other of North American Aboriginal background. Susceptibility to MS in people of mixed North

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e-Pub ahead of print on June 10, 2009, at www.neurology.org.

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Supported by the Multiple Sclerosis Society of Canada Scientific Research Foundation. S.V.R. is funded by the Medical Research Council of the United Kingdom. G.C.E. is the Action Research Professor of Clinical Neurology at the University of Oxford.

Disclosure: Author disclosures are provided at the end of the article.

American Aboriginal-Caucasian ancestry is likely introduced by the Caucasian parent. Therefore analysis of the offspring of the different mating types in this study permits the examination of maternal and paternal effects in disease etiology.

METHODS **Subjects.** The methods of the CCPGSMS have been described previously.[4] Briefly, collaborating centers across Canada used standardized, telephone-administered data questionnaires to screen individuals with MS. Information about ethnic background is routinely collected and index cases were included in this study if they had 1) 1 Northern European Caucasian parent and 2 corresponding Caucasian grandparents and 2) the other parent and both grandparents of North American Aboriginal ancestry.

Standard protocol approvals, registrations, and patient consents. Each participating clinic in the CCPGSMS obtained ethical approval from the relevant institutional review boards and the entire project was given approval by the University of British Columbia and the University of Western Ontario. Written informed consent was received from all subjects in this study.

Statistical analyses. The χ^2 distribution and Fisher tests were used to assess significance in all instances, except for when looking at age data, where a 2-tailed Student t test was used to assess significance. Sib risk was calculated as done previously, based on a modification of the maximum likelihood approach.[5]

RESULTS Fifty-eight nuclear families were identified where the MS index case had 1 unaffected parent of Caucasian ancestry and 1 unaffected parent of North American Aboriginal ancestry. Statistics Canada does not collect information regarding the ethnicity of each parent, so we could not compare this to the total number of children in Canada with 1 Caucasian and 1 North American Aboriginal parent. Of the 58 MS index cases identified through the CCPGSMS, 27 had a Caucasian mother and a North American Aboriginal father; the remaining 31 had a North American Aboriginal mother and a Caucasian father. The demographic characteristics of the affected offspring from the different mating types are shown in the table.

As shown in the table, there were no significant differences in terms of sex ratio and age of all offspring, as well as age at disease onset and clinical course of MS cases between offspring of maternal Caucasian by paternal North American Aboriginal matings and affected offspring who had a North American Aboriginal mother and a Caucasian father.

The total number of affected offspring was similar in the 2 mating types. The sex ratio of MS offspring, however, was different. Twenty-eight of 32 patients with MS who had a Caucasian mother and a North American Aboriginal father were female (female:male sex ratio 7:1) compared to a female to male sex ratio of 2:1 for patients with MS with a Caucasian father and a North American Aboriginal mother (Fisher exact test $p = 0.043$).

The age-corrected sib risk in the MS probands who had a North American Aboriginal father and a Caucasian mother (risk = 7.2%) was nearly double that of probands who had a North American Aboriginal mother and a Caucasian father (corrected sib risk = 4.1%). However, this is based on small numbers of affected siblings.

DISCUSSION MS is a complex neurologic disease with a striking geographical distribution.[6] In Canada, the prevalence of the disease is high in Caucasians of European descent,[7] but lower in the North American Aboriginal population,[8] and perhaps only increased in North American Aboriginals when there is mixed ancestry.[9] In the present study, the characteristics of patients with MS with a Caucasian mother and a North American Aboriginal father were compared to patients with a North American Aboriginal mother and a Caucasian father. The sex ratio of patients with the former parentage was significantly greater than for the latter parentage when maternal and paternal ethnicities were reversed. Similarly, the number of affected individuals by mating type was similar but this does not preclude a quantitative difference in risk. There is an anecdotal bias toward more matings in which the father is Caucasian and this has been quantitated in matings between Asians and Caucasians.[10]

We have shown that the sex ratio of MS in Canada has been increasing over the last 50 years[11] and this increase has environmental origins. There were no differences in the mean age of the patients investigated in the 2 mating groups, suggesting that the sex ratio difference is a result of ethnicity-specific, parent-of-origin environmental interactions and not just an age-related artefact. Consistent with this, the sex ratio in admixed African Americans has been shown to be approximately 6:1.[12]

A parent-of-origin effect (maternal) has been repeatedly observed in MS, based on studies of half-siblings,[5] sibships including dizygotic twins,[13] a large extended Dutch pedigree,[14] and avuncular pairs,[15] as well as a timing of birth effect.[16] The comparison of offspring from interracial matings is a novel method of analysis to look for parent-of-origin effects. As focus is shifting from the investigation of genetic factors to gene–environment interactions and epigenetic mechanisms in complex trait studies, our data highlight how admixture cohorts can be used to detect parental effects. The biologic basis of the maternal effect in MS is unknown. The data from this study hint at an intriguing possibility that the ob-

Table Clinical and demographic characteristics of affected offspring with multiple sclerosis from matings of different maternal and paternal ethnicities

	Caucasian mother and North American Aboriginal father	North American Aboriginal mother and Caucasian father
No. of families	27	31
No. of offspring, including index case	121	109
F:M sex ratio	63:58 = 1.09	57:52 = 1.10
No.*; mean age, y (SD)		
Female	63; 49.2 (12.1)	52; 42.9 (13.6)
Male	57; 48.0 (15.5)	48; 41.6 (11.0)
Total	120; 48.6 (13.8)	100; 42.3 (12.4)
No. of affected offspring, including index case	32	33
F:M sex ratio	28:4 = 7:1	22:11 = 2:1
No.†; mean onset age, y (SD)		
Female	27; 32.0 (10.5)	21; 29.6 (6.0)
Male	4; 37.4 (7.7)	11; 32.8 (11.1)
Total	31; 32.9 (10.2)	32; 30.7 (8.1)
Relapsing-remitting MS,‡ n (%)	25/28 (89.3)	21/30 (70)
Crude sib risk,§ n (%)	5/94 (5.4%)	2/78 (2.6%)
No.¶ (no. of affected)	93 (5)	69 (2)
Age-corrected risk, SE (95% confidence interval) (Kaplan-Meier estimation)	0.072 (0.029–0.166)	0.041 (0.002–0.106)

*Sex unknown for 1 child in the Caucasian mother/North American Aboriginal father group and 9 children in the North American Aboriginal mother/Caucasian father group.
†Mean age at symptom onset unknown for 1 affected child in the Caucasian mother/Aboriginal father group and 1 affected child in the North American Aboriginal mother/Caucasian father group.
‡MS course unknown for 4 affected children in the Caucasian mother/North American Aboriginal father group and 3 unaffected children in the Aboriginal mother/Caucasian father group; relapsing-remitting: bout onset with the presence or absence of later progression (secondary progressive MS).[17]
§Denominators exclude index cases.
¶Denominators exclude index cases and siblings for whom age information is unknown.
MS = multiple sclerosis.

served female preponderance of MS could result from environmental factors acting upon mothers to differentially affect MS risk more in female than in male offspring. Fathers impart susceptibility to MS, but perhaps differently than mothers. If indeed an increase in MS risk and sex ratio is partly caused by a maternal–environmental interaction, North American Aboriginal mothers may be resistant to this because of different environmental exposures than those of Caucasian mothers, for example, diet, smoking behavior, and levels of outdoor activity, or by virtue of different genetic background. The possible genetic and environmental hypotheses for our results need to be explored further.

AUTHOR CONTRIBUTIONS

Statistical analysis was performed by Dr. Sreeram Ramagopalan (University of Oxford) and Irene Yee (University of British Columbia).

ACKNOWLEDGMENT

The authors thank the patients who participated in this study.

DISCLOSURE

Dr. Ramagopalan receives research support from the Multiple Sclerosis: Society of Canada Scientific Research Foundation and the Multiple Sclerosis Society of the United Kingdom. Dr. Marrie serves as an editorial board member of *Neurology*®; receives research support from BioMS Technology Corporation, Sanofi-Aventis, Berlex, EMD Serono Canada, the Manitoba Health Research Council (PI), University of Manitoba (Rudy Falk Clinician Scientist), Health Sciences Centre Foundation (PI), Multiple Sclerosis Society of Canada (PI), Multiple Sclerosis Scientific Foundation (Co-PI), and the Consortium of Multiple Sclerosis Centers. Dr. Sadovnick has received funding for travel from Bayer Canada, the European Charcot Foundation, the MS Society of Canada, the National MS Society, and the Consortium of MS Clinics; has received speaker honoraria from Teva Scientific and the MS Society of Canada; and has received research support from the MS Society of Canada Scientific Research Foundation (Co-PI) and the CIHR (Co-PI). Dr. Ebers has received a speaker honorarium from Roche and a consultation fee from UCB Pharma and receives research support from Bayer Schering Pharma, the MS Society of the United Kingdom (grant 865 07 [PI] and grant # 875 07 [PI]) and from the MS Society of Canada Scientific Research Foundation (PI and Co-PI).

APPENDIX

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Received March 11, 2009. Accepted in final form May 7, 2009.

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