SHORT REPORT

Multiple sclerosis in stepsiblings: recurrence risk and ascertainment

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Reports implicating specific transmissible agents in multiple sclerosis (MS) susceptibility continue to appear. We therefore re-evaluated MS risk in 687 stepsiblings of 19 746 MS index cases. We found the risk of MS to be indistinguishable from that of the general population after diagnostic verification. These results are coherent with studies of adopted children, half siblings and conjugals, showing no risk attributable to the familial microenvironment. This family based genetic epidemiological approach found no trace of transmissibility other than genetic from one affected individual to another in the high prevalence area of Canada. This adds to existing data showing that the action of environment in influencing MS risk is operative at a population level.

The genetic epidemiology of multiple sclerosis (MS) has been studied in more detail than for any other complex trait. Studies from twins, half-siblings, adopted children, and conjugal MS matings have complemented highly reproducible data from familial recurrence risk studies (see review by Dyment *et al*.[1]). Taken together, these data have led to the prevailing concept of MS as a complex trait determined by genes and environment, both of which may themselves be heterogeneous and complex. The notion of a large number of genes with small effect as the fundamental basis for susceptibility has been repeatedly suggested, often in conjunction with negative genotyping results. However, there is little direct evidence for this concept and there are increasing indications that it deserves a more critical appraisal.[1] In addition, a recent half sibling study[2] indicates an as yet unspecified maternal effect, and some suggestion of an impact of birth timing is found in the slightly greater MS risk for dizygotic twins compared with non-twin siblings.[3] The nature of these observations remains uncertain.

Several decades of effort in trying to identify a causative virus for MS have seen reports of several specific viral isolations undone. However, if the notion that the disease is caused by a transmissible agent has gradually yielded, it is not evident from unabated reports implicating one or other infectious agent.[4] The extensive resources of the Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS) have failed to show support for the concept of non-heritable transmissibility during adulthood[5] or childhood,[2 6] using the classic tools of genetic epidemiology.

We have previously reported results that address the question of transmissibility and that have spanned, systematically and with overlapping perspective, the periods of time up to the usual ages of disease onset. The first was an adoption study,[6] which gave a clear indication that familial risk was not determined by the common familial microenvironment dating from shortly after birth. Similarly, studies of half siblings[2] showed no risk attributable to common childhood habitation, and a large study of conjugal risk[5] showed no increased risk through common exposure in the adult years. Although less powerful, studies of birth order in single[7] and multiply affected families[8] have been negative, but these findings are perhaps not yet definitive. Studies that have cast considerable doubt on the concept of non-heritable transmissibility are usually not mentioned or explained in papers making a case for viral infection. The hypothesis that genetic background determines disease response to a ubiquitous infection remains viable, but has little discriminatory value as it can be made for any blanket environmental exposure.

Another way to examine the influence of common environment is a study paradigm similar to the evaluation of adoptee risk. The study of stepsiblings who have ''migrated'' into families in which at least one of the children subsequently developed MS would represent such a strategy. We have thus examined the recurrence risks for MS in this population, with the prior expectation that there would be no increased risk for these stepsiblings compared with the general population, based on results of the half sibling[2] and adoptee[6] data.

MATERIALS AND METHODS

The CCPGSMS has been described in several publications.[2 3 5 6] It is essentially a population based sample from the 14 MS clinics spread across Canada. The longitudinal nature of the CCPGSMS data has allowed much interclinic and intraclinic validation of ascertainment. As part of data collection, 19 746 index cases were asked about biological (full, half) and non-biological (adopted, step) siblings. In total, 687 stepsiblings were consecutively ascertained in this manner, form the basis of the study reported here.

MS status (''affected''/''unaffected'') was sought for the 687 reported stepsiblings according to CCPGSMS protocol described in other publications[2 3 5] and in accordance with the Poser Committee criteria.[6] For all reportedly affected stepsiblings of index cases, it was possible to either examine the individual or scrutinise medical records to determine the ''best estimate'' diagnosis, again as described in previously published family studies on the CCPGSMS population[2 3 5] and in accordance with Poser Committee criteria.[6] We then examined the nature of the family structure and looked for the presence of MS in both biological and non-biological relatives.

Under the null hypothesis, the risk of a stepsibling to have MS is 0.001 (population point prevalence) and the significance level is assumed to be 0.05. Our study sample of 687 had the power of about 0.80 to detect four or more affected stepsiblings (4/687 = 0.00582, power = 0.762; 5/687 = 0.00727, power = 0.875).

RESULTS

Four stepsiblings were reported to have MS by CCPGSMS index cases. This appeared to represent a substantial increase over that expected based on the general population rate.

Abbreviation: MS, multiple sclerosis

Detailed medical records, obtained with the individuals' consents, clearly did not confirm a diagnosis of MS for two stepsiblings who in fact had no history of any neurological signs or symptoms suggestive of MS or any other neurological condition. In one additional stepsibling, the diagnosis of MS was listed among possible differentials many years previously, based on minor sensory symptoms and the fact that a stepsibling had MS. However, in this individual, consecutive head and spinal MRI results were negative and the individual has remained clinically asymptomatic. MS was confirmed in 1/687 stepsiblings, for a risk of 0.15% (95% CI 0.00 to 0.43%). Of the 143/687 stepsiblings who lived together before the age of 15 years, none has developed MS. An additional 207 stepsiblings had some contact with the index case prior to 15 years of age, but did not actually live together. Of these, 35 had monthly contact or more, 62 were together several times over each year but less than monthly, 43 had contact once each year, and 67 had occasional contact. The remainder of the stepsiblings (337/687; 49.1%) only had contact with the index case during adulthood. The one stepsibling with MS established contact with the index case only after 21 years of age.

DISCUSSION

To our knowledge, this study is the first to look at familial aggregation of an inflammatory/autoimmune disease within stepsiblings, including diseases where an infectious agent has a more established role than in MS.

The preliminary raw results from this study unexpectedly suggested a several fold elevation in recurrence risk for stepsiblings compared with the general population. This was not borne out by examination of the specific individuals, as the apparently elevated risk was related to unverifiable diagnoses. There were no cases of MS among 350 stepsiblings who either cohabited or had limited contact with MS index cases up to the age of 15 years. It must be remembered that the critical nature of that age is based on small numbers from migration studies and that the largest study to date on this topic in fact extends the age period for alteration of MS risk into the 20s.[9]

A possible ascertainment bias could have been the impact of assortative mating if one (or both) stepparent(s) had MS, thus introducing stepsiblings with a higher genetic susceptibility compared with the general population. However, we did not encounter any examples of this occurring in the present study.

The results presented here once again demonstrate the importance of ascertainment and of detailed scrutiny of reportedly affected family members with respect to diagnosis. The undoing of diagnoses in the few reported cases of MS in these families contrasts with the relative reliability of diagnoses in the biological relatives we have studied for many years, where the accuracy of reporting appears to be higher.

CONCLUSION

Stepsibling results, which initially seemed to be inconsistent with prior data, were found on closer examination to be coherent with the findings from adoptee, half- sibling, and conjugal data. After removal of three cases where the clinical diagnosis was not supported and with negative investigation, only one case out of 687 remained. Thus, 1/687 is closer to the true stepsibling risk.

The numbers of stepsiblings were necessarily small and we concede that they do not exclude an increased risk. However taken in conjunction with data from other CCPGSMS special case comparisons[2 3 6] where the impact of shared early life environment can be assessed, our data provide additional support for the view that MS risk is unaffected by the familial microenvironment throughout life and that important non-genetic factors act at a broad population level to influence risk. The data further illustrate the necessity of considering the impact of ascertainment on epidemiological findings. The one aspect of risk in which stepsiblings may extend previous results more specifically is the suggestion raised in one paper that MS is related to childhood sexual abuse.[10] As stepchildren (in the context of this paper, the stepsibling of the index case) are among the most frequent victims (in the context of the current paper, this would refer to one of the biological parents of index cases), this hypothesis would be perhaps viewed as being supported if we had found any instances of stepparent to stepchild transmission. However, clearly neither this study nor prior studies of adoptees[6] and half siblings[2] show even a trace of a common familial effect. Any further claims of infective causes of MS would need to take these data in account.

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REFERENCES

1 **Dyment DA**, Ebers GC, Sadovnick AD. Genetics of multiple sclerosis: 2003 update. *Lancet Neurology* 2004;**3**:104–10.
2 **Ebers GC**, Sadovnick AD, Dyment DA, Yee IML, Willer CJ, Risch N, Canadian Collaborative Study Group. A parent of origin effect in multiple sclerosis: observations in half siblings. *Lancet* 2004;**363**:847–50.
3 **Willer CJ**, Dyment DA, Sadovnick AD, *et al*. Twin concordance and sibling recurrence rates in multiple sclerosis. *PNAS* 2003;**100**:12877–82.
4 **Swanborg RH**, Whittum-Hudson JA, Hudson AP. Infectious agents and multiple sclerosis—are Chlamydia pneumoniae and human herpes virus 6 involved? *J Neuroimmunol* 2003;**136**:1–8.
5 **Ebers GC**, Sadovnick AD, Risch NJ, the Canadian Collaborative Study Group. Familial aggregation in multiple sclerosis is genetic. *Nature* 1995;**377**:150–1.
6 **Poser CM**, Paty DW, Scheinberg L, *et al*. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;**13**:227–31.
7 **Gaudet JPC**, Hashimoto L, Sadovnick AD, *et al*. A study of birth order and multiple sclerosis in multiplex families. *Neuroepidemiology* 1995;**14**:188–92.
8 **Gaudet JPC**, Hashimoto L, Sadovnick AD, *et al*. Is multiple sclerosis caused by late childhood infection? A case-control study of birth order in sporadic cases of multiple sclerosis. *Acta Neurol Scand* 1995;**91**:19–21.
9 **Hawkes CH**. Is multiple sclerosis a sexually transmitted infection? *J Neurol Neurosurg Psychiatry* 2002;**73**:439–43.
10 **Hammond SR**, English DR, McLeod JG. The age-range of risk of developing multiple sclerosis: evidence from a migrant population in Australia. *Brain* 2000;**123**:968–74.