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REVIEW

Differential effects of genetic susceptibility factors in males and females with multiple sclerosis

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Abstract Multiple sclerosis (MS), a putative autoimmune disease, has a well documented female preponderance among patients. However, this is not the only sex effect observed in the disease. Unaffected mothers appear to be at a higher risk to transmit susceptibility (genetic, environmental or interactions thereof) compared to unaffected fathers. This maternal effect can range from intrauterine exposures to transmission of genotypes and epigenetics.
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1. Introduction

Multiple sclerosis (MS), a putative autoimmune disease, is the most common cause of non-traumatic neurological disorder affecting young adults. The disease is characterized by myelin loss and axonal degeneration and as with almost all common complex traits, genetic and environmental components have important roles, both independently and interactively, in disease susceptibility [1,2]. As with most if not all autoimmune diseases, MS shows a sex predilection, although this was unclear until the 1920's. Early estimates of the sex ratio in MS showed this to be close to unity or perhaps even higher in men. Weschler reported a case series of 1970 (1773 cases from the literature plus 197 cases whose records the author personally reviewed) and found that the male:female sex ratio for disseminated sclerosis was approximately 3:2 [3]. However, by the 1940's, the male predominance of the disease was disputed and a 1:1 sex ratio declared in an official statement by the National MS Society [4]. However, over time, it became recognized that there was indeed a female predominance among MS patients. By the mid-1970's, a review of 14 MS prevalence studies gave a sex ratio of 1.4:1 [5]. In the 1980's and 1990's, evidence supporting a female preponderance continued with the agreement that the female to male sex ratio was approximately 2:1 [6,7].

Interest in the sex ratio of MS has increased in recent years although not to dispute the female preponderance. Rather, reports have suggested that the rate of MS is increasing but it remained a conundrum whether this was a true increase or a reflection of various artifacts including earlier diagnosis and changing diagnostic criteria allowing magnetic resonance imaging (MRI) findings to be factored in [8–10]. As part of the population-based Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS) [11], it was decided to look at sex ratio by birth years as a surrogate of incidence change [12]. The results showed that the sex ratio was increasing by the year of birth ($p < 0.001$, $\chi^2 = 124.4$, rank correlation $r = 0.84$), thus the year of birth was a significant predictor for sex ratio — see Fig. 1. The data also showed that the findings were driven by an increase in the MS rate in females and not a decrease in males [12]. This rapid change is interpreted to have environmental origins even if it is associated with a gene–environment interaction thus suggesting that a large proportion of MS may be preventable. Subsequent studies have largely supported these findings [13–15] with a notable exception being from Sweden [16].

From large studies, it is clear that the environmental factors are population and geographically based rather than intra-familial [17–20]. Strongly indicated candidates include the Epstein–Barr virus (EBV) [21], vitamin D measured by serum 25-hydroxyvitamin D (25(OH)D) levels [22–27], and smoking [28,29]. Recently, obesity as measured by body mass index (BMI) [30] has been implicated as a risk factor for MS in both adult and pediatric cases [30]. Although the mechanisms remain unclear, this appears to impact females rather than males [31–35]. Further evidence for the contribution of environment is from migration studies. [36,37].

2. Maternal effect + MS susceptibility

While the sex effect in MS characterized by the female preponderance is well established, longitudinal research

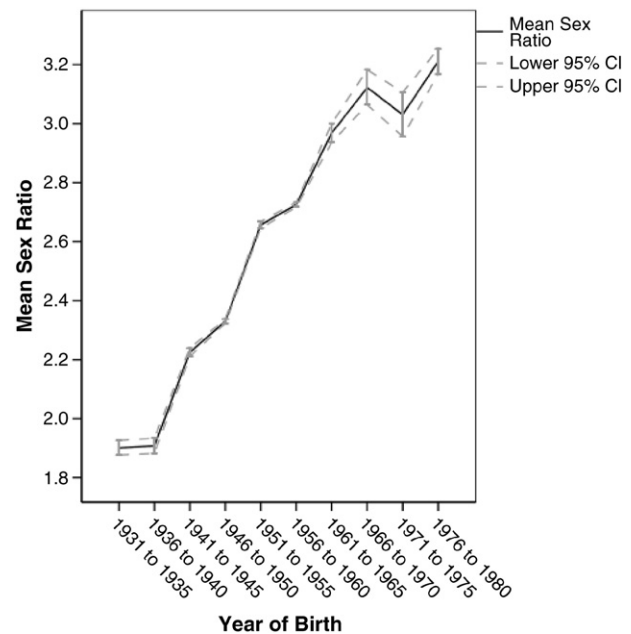


Figure 1 Sex ratio by the year of birth [12].

over time has suggested another “sex effect” imparted by the unaffected mothers of MS patients. The initial hint of a material effect was observed in the first study of half-siblings with MS [18] where a non-significant ($p > 0.05$) trend showed that maternal half-siblings were more often concordant for MS compared to paternal half-siblings. However, a subsequent larger study [19] found this to be statistically significant (34/1859 (1.8%) maternal half sibs had MS compared to 15/1577 (0.9%) paternal half sibs; $p = 0.048$). Further support for the maternal effect in MS susceptibility has come from studies of (i) avuncular pairs [38], (ii) DZ twins vs. sibs in same sibship [39], (iii) an isolate from the Netherlands [40] and (iv) inter-racial matings [41].

2.1. Avuncular pairs

As part of the CCPGSMS, a cohort of 807 avuncular MS families with 938 affected aunt/uncle, niece, nephew (AUNN) pairs was ascertained, we examined differential MS transmission by separating affected pairs into a likely maternal (through mother of the CCPGSMS index case) and paternal (through father of the CCPGSMS index case) origin [38]. The number of avuncular pairs connected via an unaffected mother is significantly higher compared to pairs connected via an unaffected father (526 vs. 412, McNemar's $\chi^2 = 6.95$, $p = 0.008$). To restrict confounders introduced by families with multiple pairs (more than one affected niece/nephew, more than one aunt/uncle), the overall number of maternal families was compared to the overall number of paternal families and we found the number of maternal families to still be significantly higher 488 vs. 370 (McNemar's $\chi^2 = 4.28$, $p = 0.038$). This observation independently confirmed previous findings of a “maternal parent-of-origin” effect in multiple sclerosis (MS) susceptibility. These findings also independently confirm the increasing rate of MS in

females, demonstrating that familial cases are influenced by the same environmental factors as the general MS population.

2.2. DZ twins vs. sibs in same sibship

Dizygotic (DZ) twins and full siblings share 50% of their genetic material but DZ twins share the maternal uterine environment at the same point in time whereas full siblings share this at different time points. Again, as part of the CCPGSMs, we therefore looked into sibships from the CCPGSMs in which there was a DZ pair (at least 1 with MS) and other non-twin siblings [39]. We compared the concordance for MS between these two groups of siblings and found that among the DZ pairs, 5.4% were concordant for MS whereas only 2.9% of the non-twin siblings in these same sibships were concordant. These data suggest again that the maternal uterine environment can have an impact on MS susceptibility.

2.3. Isolate from the Netherlands

A large extended Dutch pedigree with multiple cases of MS, dating back to the 18th century, was studied with respect to maternal and paternal transmission patterns [40]. The results consistently indicate a higher prevalence of maternal transmission of MS. 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).

($p < .001$). This skewed relationship was again interpreted as evidence for a material effect in MS with the most likely explanation being a gene–environment effect that takes place in utero.

2.4. Inter-racial matings

As part of the CCPGSMs [11], 58 MS probands were identified who had 1 Caucasian and 1 North American Aboriginal parent. 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. 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 the detection of parent-of-origin effects in admixture cohorts.

3. Sex and gender influences on genetics of MS

3.1. Gender + the X chromosome

Several mechanisms have been proposed as explanations for the female preponderance in MS, including an increased frequency of skewed X inactivation [42]. As part of the CCPGSMs [11], 726 relative pairs including 552 affected sib-pairs were genotyped for 22 X-chromosome microsatellite markers and a novel dataset of 195 AUNN affected pairs was genotyped for 18 markers [43]. Parent-of-origin effects were explored by dividing AUNN families into likely maternal and

paternal trait transmission. For the sib-pair dataset, we were able to establish exclusion at a $\lambda = 1.9$ for all markers using an exclusion threshold of $\text{LOD} \leq -2$. Similarly, for the AUNN dataset, we established exclusion at $\lambda = 1.9$. For the combined dataset we estimate exclusion of $\lambda = 1.6$. We did not identify significant linkage in either the sib-pairs or the AUNN dataset nor when datasets were stratified for the presence/absence of the HLA-DRB1*15 allele or for paternal or maternal transmission. This comprehensive scrutiny of the X-chromosome suggests that it is unlikely to harbor an independent susceptibility locus or one which interacts with the HLA. Complex interactions including epigenetic ones, and masking by balanced polymorphisms are mechanisms not excluded by the approach taken. The most recently published large scale GWAS on MS [44] did not highlight any region of the X chromosome.

3.2. Gender + HLA DRB1

Among Caucasians, adults, while recent GWAS have identified many candidate genes [44], none to date approaches the risk factor for MS attributed to HLA interactions. Gender can influence HLA in a variety of ways. Female MS patients carry the HLA-DRB1 more often than do males (63% compared to 53%) [45–47].

In a study of 7334 individuals from 1515 MS the CCPGSMs [11 HLA-DRB1*15] was significantly over transmitted by unaffected mothers ($r = 2.89$) compared to unaffected fathers ($r = 2.07$, $\chi^2 = 7.73$, $p = 0.0054$). These data suggest that parent of origin effects at the MHC determine susceptibility to MS [47].

A more recent study, also using CCPGSMs data examined MHC transmission by family structure and gender stratified by genetic distance of affected relatives from the MS proband. Affected individuals with HLA-DRB1*15-positive genotypes had a higher female-to-male ratio compared with affected individuals with HLA-DRB1*15-negative genotypes ($\chi^2 = 9.97$, $p = 0.0015$) with the exception of multiplex families with 3 or more affected across 2 generations [48]. Transmission disequilibrium test results show that HLA-DRB1*15 transmission was more distorted in collateral families (affected individuals in the same generation e.g. siblings, 1st cousins) compared to multi-generational families ($\chi^2(2) = 8.030$, $p = 0.0046$), exclusively in affected female–female pairs ($\chi^2(2) = 7.81$, $p = 0.0051$), but not in mixed gender pairs ($\chi^2(2) = 1.58$, $p = 0.21$) or matched male pairs (Fisher $p = 0.21$). These observations suggest the MHC as the site of interactions and modifications mediating the sex ratio in MS and this may occur through gene–environment interactions and epigenetic modifications in this region [49].

The mechanism of the parent of origin effects at the MHC remains to be determined. One possibility could be sex-specific epigenetic mechanisms [50].

4. Gender correction and MS risk factors

It is often forgotten that studies looking at risk factors for MS must take gender influences into account when comparing male and female cases as well as family controls. This is critical when using spouse controls since, given the preponderance of females with MS, the majority of spouses will be

Table 1 Sibling age-adjusted recurrence risks for MS by gender of index case ^a.

	Total number	Number with MS	Percentage risk for MS	Standard error (SE)
Sisters of Female index case, i.e. same gender	1261	45	5.09	0.75
Brothers of female index case, i.e. different genders	1234	14	1.72	0.46
Sisters of male index case, i.e. different genders	398	9	3.27	1.08
Brothers of male index case, i.e. same genders	402	10	3.88	1.21

^a Adapted from [48].

male. Looking at risk factors must compensate for this. For example, recent studies on birth weight, gestational age, and r and exposure to infections as risk factors would have erroneously found differences between cases and controls if the two groups were compared without stratification for gender [51–53].

Two recent publications from the CCPGMS [51,54] have clearly validated and quantified the qualitative impression of experienced medical practitioners that there is a sex-specificity of recall and reporting bias as well as a greater female awareness of medical history. Specifically for MS, it was found that males, regardless of whether they were index cases or spousal controls, were consistently more uncertain of their infection or vaccination history than were females. As well, males significantly under-reported disease in themselves and their first degree relatives compared to females.

5. Gender and MS recurrence risks

Data suggest that sexually dimorphic liability factors operate MS susceptibility [55]. Table 1 gives age-corrected and gender-specific MS recurrence risk data for the siblings of MS patients. The highest risk (5.09%) is for female/female pairs. Note that these risks shown in Table 1 can increase significantly for varying familial structure, i.e. siblings are offspring of conjugal MS pairs (45), or the unaffected parents are first cousins [56,57].

Given the higher prevalence of MS in females, it has been hypothesized that affected males had a higher genetic load and thus their offspring would be at a greater risk for MS [58]. However, in CCPGMS data [11], affected mothers and

fathers were equally likely to transmit MS to their offspring (see Table 2a and b) [55]. In addition, the sex ratio among affected offspring was the same, regardless of whether the transmitting affected parent was a mother or a father [55,59].

6. Summary

In summary, sex and gender influences in MS expand beyond the scope of sex ratio and can contribute to our understanding of the pathogenesis and natural history of MS and hopefully ultimately to the treatment of this disease. The papers in this supplement should provide an excellent, up-to-date, evidence-based review of “Sex Influences in Auto-immune Disease”.

Conflict of interest statement

The author(s) declare that there are no conflicts of interest.

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Table 2 Affected parent gender and transmission of MS to offspring ^a.

a: Affected offspring ^a				
Parent with MS	Affected daughters	Affected sons	Total affected offspring	Sex ratio for affected offspring
Mothers with MS	404 (71.13%)	164 (28.87%)	568 (100%)	2.46
Fathers with MS	159 (70.67%)	66 (29.33%)	225 (100%)	2.41
b: Unaffected offspring ^a				
Parent with MS	Unaffected daughters	Unaffected sons	Total unaffected offspring	Sex ratio for unaffected offspring
Mothers with MS	2558 (48.69%)	2696 (51.31%)	5254 (100%)	0.95
Fathers with MS	1034 (47.76%)	1131 (52.24%)	2165 (100%)	0.91

^a Adapted from [48].

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