The Increased Susceptibility of Women to Multiple Sclerosis

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ABSTRACT: Many diseases with an auto-immune etiology have a skewed sex distribution. In the majority of instances, women are affected more frequently than men. A review of population studies demonstrates that the preponderance of women in multiple sclerosis (MS) is almost constant. We show that this preponderance is further increased in early as well as in late-onset cases, in familial cases as well as in MS twin pairs and that the HLA-DR2 allele, which has been associated with MS in Caucasian populations, is significantly more frequent in women than in men with MS. "Rules" have been established for multifactorial diseases; MS contravenes most of those rules. The skewed sex distribution in MS could be attributed to the known hormonal and gender influences on the immune response, as well as to genetic influences.

RÉSUMÉ: Prédisposition accrue des femmes à la sclérose en plaques. La plupart des maladies de type auto-immun ont une répartition inégale selon les sexes. Le plus souvent, plus de femmes que d'hommes sont plus atteintes. Une révision d'études épidémiologiques démontre que les femmes sont constamment plus fréquemment atteintes de sclérose en plaques (SEP) que les hommes. Nous montrerons que cette prépondérance féminine est accrue dans les formes précoces, comme dans les formes tardives de la maladie, dans les formes familiales et chez les couples de jumeaux. De plus, l'allèle HLA-DR2, associé à la SEP dans les populations de race caucasienne, est significativement plus fréquent, dans cette maladie, chez les femmes que chez les hommes. Des règles régissant les maladies multi-factorielles ont été décrites; la SEP n'en respecte presque aucune. La prépondérance féminine dans la SEP pourrait être attribuée aux influences connues des hormones sexuelles sur les réponses immunes, ainsi qu'à des facteurs génétiques.

Can. J. Neurol. Sci. 1992; 19: 466-471

Diseases not involving the genital organs and their appendages should, in theory, be equally distributed among women and men, if exposure to the causative agents is the same. They are not. Multiple sclerosis (MS) is one of many diseases with a skewed sex distribution. The disease is clearly more frequent in women than in men,[1] but this observation remains largely unexplained. The explanation is probably related to the etiology and many hypotheses have been formulated, but none can be substantiated. Most diseases with a known or alleged auto-immune etiology have an unbalanced sex distribution;[2] in a majority of cases, women are affected more often than men. Lupus erythematosus is nine times more frequent in women than in men,[3] thyroid diseases are more frequent in women,[4] so are rheumatoid arthritis[5] and myasthenia gravis.[6] Ankylosing spondylarthritis is four to nine times more frequent in men,[7] as is periarteritis nodosa.[8] Sex hormones are thought to influence immune responses.[2] For example, there are rat strains with a spontaneous disease very similar to lupus which occurs exclusively in females. When females are castrated before puberty, or given male hormones, the disease is prevented; when male rats are given female hormones, they become susceptible to the disease.[2] Tropical spastic paraparesis is more frequent in women,[9] and this apparently cannot be accounted for by distinct exposure patterns. Seemingly, men and women, for obscure reasons, react differently to a variety of disease agents. This seems worthy of attention. This paper intends to firmly document the greater frequency of MS in women, to show that this is even more apparent in some categories of the disease, to document that MS contravenes the "rules" formulated for multi-factorial diseases[10] and to discuss the hypotheses put forward to account for the unbalanced sex ratio.

Materials and Methods

We have reviewed published data, including our own. Twenty-nine epidemiological studies have been summed,[11-39] as well as twelve family studies[40-51] and six twin studies.[52-57] Rules for multi-factorial diseases have been borrowed from Childs and Scriver.[10]

Results

Epidemiological Studies

Most epidemiological studies mention that MS is more frequent in women than in men. Thirty surveys originating from 18

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Received October 28, 1991. Accepted April 13, 1992.
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countries and dating from 40 years onwards[11-39] indicated that, from a total of 15,988 patients, 10,202 were women and 5,786 were men, for a woman to man ratio (W:M) of 1.76:1. Only one survey reported a higher figure for men.[33] In the Canadian population, recruited from 13 MS clinics, from a total of 4,632 patients, 3,118 were women, 1,514 were men, for a W:M of 2:1.[58] Data from individual studies are given in Tables 1 and 2. There is a tendency for older studies to show a more equal sex distribution, while the preponderance of women is more apparent in recent surveys. It has been established that women seek medical attention more often than men do.[59,60] But also, it is conceivable, with increasing numbers of neurologists and with technological improvements, that a greater proportion of benign cases are ascertained and these are more frequent in women (see below).

We have previously published that early-onset cases are even more common in women than in men.[58] Of 499 patients whose MS began before age 20, 381 were women, while 118 were men, for a W:M of 3.2:1. When compared to the ratio of 2:1 for the Canadian population from which it was extracted, the p value is significant at a level of 0.000 000 001. In the early-onset cohort, there was an increased proportion of benign and of relapsing-remitting cases. This higher frequency of women in early-onset cases probably explains why the average age of onset is usually one year earlier in women than in men in large epidemiological studies.

Table 1. Summary of Thirty Incidence — Prevalence Studies on MS

Authors	Year	Country	Population Total	F	M
Sutherland	1956	Northern Scotland	127	71	56
Alter	1962	Israel	282	147	135
Saint	1962	Western Australia	98	54	44
Stazio	1964	Winnipeg, Man., Canada	128	88	40
Chipman	1966	Houston, Texas, USA	67	45	22
Oltedel	1966	Vestfeld, Norway	127	71	56
Presthus	1966	Romsdal County, Norway	81	40	41
Rischbreth	1966	South Australia	351	211	140
Dean	1967	South Africa	281	198	83
Stazio	1967	New Orleans, Louisiana	59	34	25
McCall	1968	Australia (Perth,..)	236	148	88
McCall	1969	West Australia	122	85	37
Percy	1971	Rochester, Minnesota	48	33	15
Dean	1976	London, GB (Immigrants)	3970	2511	1459
Bennett	1977	Ottawa, Ont., Canada	222	155	67
Brady	1977	Republic of Ireland	1951	1133	818
Detels	1977	USA (Japanese American)	15	8	7
Poser	1978	Lower Saxony, Germany	812	520	292
Sheperd	1978	North East Scotland	557	343	214
Kurtske	1979	Faroe Islands	14	8	6
Hoffman	1981	Los Alamos, New Mexico	27	18	9
Granieri	1982	Southern Italy	21	11	10
Hader	1982	Saskatchewan, Canada	201	135	66
Kurtzke	1982	Iceland	165	99	66
Gallow	1983	Britain (France)	602	397	205
Granieri	1983	Insular Italy	31	18	13
Kinnunen	1984	Finland	548	350	198
Larsen	1984	Western Norway	236	145	91
Granieri	1985	Ferrara (Italy)	176	108	68
Duquette	1988	Canada	4632	3118	1514
TOTAL			15988	10202	5786

Late-Onset Cases

Late-onset cases have their initial manifestations after age 45. Noseworthy has described a late-onset MS population from London, Ontario.[61] From a total of 606 cases, MS began in 527 before age 51, with a W:M of 2:1, while MS began in 79 after age 50, with a W:M of 2.4:1 (p value for the difference: 0.45). In Poser's study,[32] from a total of 812 cases, MS began in 84 before age 45 or after, with a ratio of 2.7:1 (p value for the difference: 0.0118). The W:M for the whole Poser's cohort was 2:1. This statistically significant increase of the susceptibility of women to MS in the early and in the late-onset groups could be related to puberty and to menopause. In our MS clinic woman population, the age of puberty is spread between ages of 10 and 16 and the age of menopause is spread between ages of 40 and 56, a normal distribution in both cases. The age of puberty is more difficult to determine with precision in men, but we have not noticed, nor has it been reported, that there is a clear difference from the norm in our MS population.

Familial Cases

Table 2 lists data from 12 published studies of familial MS.[40-51] Overall, 755 individuals were evaluated, 413 women and 342 men (W:M of 1.2:1). 483 were considered clinically unaffected, 237 women and 246 men (W:M of 0.9); 272 were considered as having definite or probable MS, with a W:M of 1.8:1. In 24 families with more than one member with MS from our clinic, 62 individuals were considered as having definite or probable MS, 43 women and 19 males, for a W:M of 2.2:1.

Sadovnick et al. have reviewed the influence of gender on the susceptibility to MS in sibships recruited from two large Canadian MS Clinics.[62] They have not found an increased incidence of like-sexed pairs of relatives concordant for MS. There was no increase in extended HLA-haplotype sharing among members of like-sexed pairs. They conclude that their data does not provide evidence for a relationship between sex and disease susceptibility in relatives concordant for MS. Weitkamp had

Table 2. Summary of Familial MS in 13 Epidemiological Studies

Authors	Families Seen	Individuals Seen Total	F	M	Affected Total	F	M
Alter (1976)	7	43	23	20	17	13	4
Barroche (1986)	6	22	12	10	12	8	4
Bird (1975)	1	49	16	33	3	1	2
Drachman (1976)	8	33	13	20	17	9	8
Eldridge (1978)	7	48	27	21	19	11	8
Ekbom (1966)	3	23	9	14	8	4	4
Hens (1978)	11	41	18	23	23	9	14
Olsson (1976)	5	22	12	10	11	6	5
Pratt (1951)	15	72	40	32	33	23	10
Stewart (1981)	13	95	53	42	29	19	10
Turpin (1986)	5	31	15	16	11	7	4
Visscher (1979)	12	53	38	15	27	23	4
Duquette (1988)	24	223	137	86	62	43	19
Total	117	786	423	363	272	176	96

https://doi.org/10.1017/S0317167100041664 Published online by Cambridge University Press

reported an increased proportion of like-sexed pairs in relatives with MS.[63]

Twin Studies

Several large twin studies have now been reported.[52-57] They all indicate an increased concordance rate for monozygotic twin pairs. Twin studies tend to be biased towards homozygosity and concordance, but this bias can be alleviated by an appropriate recruitment process. It is possible, although not demonstrated, that same sex women twin pairs are more easily recruited than same sex men twin pairs, since women usually collaborate more readily than men do. Consequently, it is conceivable that part of the excess of women in twin studies is due to a recruitment bias, but we doubt that it accounts for the magnitude of the imbalance we are reporting. From a total of 162 reported twin pairs with a specified sex distribution, 78 were monozygotic (W:M 3.8:1) and 84 were dizygotic (W:M 2.7:1). Of 15 monozygotic concordant pairs, 12 were women, three were men, for a W:M of 4:1 (Table 3). Unfortunately, even after inquiry, sex distributions were not available for all reported twin pairs. For this reason, Table 3 does not mention sex distribution.

In a study of US male war veterans, out of 21,000 charts of male twins, only 16 MS cases were found in 15 male twin pairs.[64] An additional veteran had an isolated optic neuritis. This is less than half the expected prevalence in a comparable control population. This brings some indication that maleness has a protective effect on susceptibility towards MS. In addition, the percentage of positive family history among family members of MS twins is very high, from 50% to 60%, in studies that have evaluated this aspect.[65,52] Somehow, it would seem that gender, twinning, disease transmission among family members and susceptibility to MS are related. This could be an expression of the multiple genes now thought to be involved in the etiology of MS.

HLA-DR2 Distribution According to Gender

The major histocompatibility complex is a highly polymorphic set of genes situated on the short arm of chromosome 6. Among many functions, it determines HLA-alleles, i.e., transmembrane glycoproteins found on the surface of all nucleated cells. Many disease associations with HLA-alleles have been described, mainly with auto-immune disorders. MS has been linked, in Caucasian populations, with DR2 and later with DQw1.[66] Since chromosome 6 is of the somatic type, its alleles should be equally distributed between sexes. Table 4 describes the distribution of a few HLA-alleles in two MS populations; we have calculated and reported that the HLA-DR2 allele is more frequent in women than in men and that the difference reaches statistical significance in the London, Ontario cohort.[67] Similar uneven distributions of HLA-alleles according to sex have previously been reported in MS,[68] in ankylosing spondylitis (in a Pima Indian tribe),[69] in myasthenia gravis,[70] as well as in lupus erythematosus.[71] Possible explanations for this paradox could be the following: interaction between sex and the genes responsible for the major histocompatibility complex; modulation of the immune response by sex factors (genes or hormones); clinical heterogeneity of the disease (there would be, in these groups, an overrepresentation of a particular form of MS, more frequent in women).

Rules for Multifactorial Diseases

Childs and Scriver have proposed rules applying for multifactorial diseases.[10] Since a prevailing hypothesis holds that MS is a multifactorial disease, with an unspecified environmental agent acting on an hereditary predisposition,[1] MS should abide by those rules. The main rules are the following:

Cases of early onset are more likely to have affected first-degree relatives. In our early-onset group, the percentage of

Table 3. Summary of 6 Epidemiological Studies on Twins

Author	Country	Total	Monozygotic		Dizygotic	
			Concord.	Non-conc	Concord.	Non-conc
Bobowick (1978)	U.S.A. (Veteran)	9	1M	4M	0	4M
Cendrowski (1973)	Poland	5	0	0	0	2W, 3M
Currier (1982)	U.S.A.	51	8	14	3	26
Ebers (1986)	Canada	70	7	20	1	42
Kinnunen (1987)	Finland	21	1W	4W, 6M	0	8W, 2M
Williams (1986)	U.S.A.	24	6	5W, 1M	2	6W, 4M

Table 4. Distribution of HLA According to Sex

HLA Alle le	Montreal				London, Ontario			
	Patients		Controls		Patients		Controls	
	% M	% F	% M	% F	% M	% F	% M	% F
A3	26.9	39.8	28	27.6	29.5	30.3	30.9	29.7
B7	30.7	37.3	23.8	18.6	37.7	47.9	24.5	22.4
DR2	43.2	53.2*	23.3	19.6	35.7	62.2+	30.9	29.7
DR3	31.1	26.6	14	21.7	36.1	24.4	30.6	24.3

* P = .4
\+ P < .008

https://doi.org/10.1017/S0317167100041664 Published online by Cambridge University Press

patients with a positive family history is 17%, which is less than the 20% figure reported in a Canadian study.[58]

Cases of early onset should express the disease more severely. In the same group, after an average duration of disease of 15 years, 76% of patients were not restricted to a wheel-chair, thus indicating a rather mild to moderate course.

Early onset, severity and increased incidence of affected relatives should characterize cases of the less frequently affected sex. In our study, women were much more frequently affected in the early-onset group and their evolution was milder. There was also an excess of women if all affected members of MS families were pooled, as mentioned in 3.

Late-onset cases are milder, more readily preventable, more responsive to treatment. In MS, late-onset cases have a more rapidly progressive evolution than earlier onset cases[18] and do not respond better to treatment than other groups.

Concordant twin pairs are more likely to have a positive family history. This is true for MS, as indicated in 4.

Only one of five rules applies in MS. Either the rules are non valid, or MS is not a multifactorial disease.

Discussion

In summary, we have documented the preponderance of women in the distribution of MS according to gender and presented evidence that this preponderance is further increased in early and late-onset cases, in familial cases and in twins; in addition, the HLA-DR2 allele is significantly more frequent in affected women than in affected men. We have shown that only one of five rules proposed for multifactorial diseases applies for MS. In a way, the increased susceptibility of women to MS "overrides" all other susceptibility factors and seems to be an important element in the predisposition to the disease.

Hormonal factors are usually proposed to explain skews in gender distribution, especially for auto-immune diseases. Although immune abnormalities, the most consistent being an excess production of immunoglobulins in the cerebrospinal fluid, have been described,[1] MS has not been proven to be an auto-immune disorder. The putative antigen(s) against which the elevated antibodies are directed has (have) not been identified. In addition, MS is not associated with other auto-immune diseases, as is commonly the case for diseases in that category; autoantibodies, a feature common to auto-immune disorders, have not been found in MS patients. Hormonal disturbances have not been reported either and our clinical experience with MS has not revealed obvious evidence of gonadal dysfunction. In particular, when evaluating the diseases associated with MS (as part of another study, to be submitted), we have not encountered an unexpected number of patients with ovarian disease, menstrual irregularities, decreased fertility, miscarriages, or with a primary sexual dysfunction. Another indication that sex hormones may be involved in the pathogenesis of MS is that clinical manifestations in women often run in parallel with changes in the estrogen-luteinizing hormone balance as occur during the menstrual cycle, after pregnancy and during the climacterion.[72]

It could then be assumed, given the apparently normal status of gonadal function, that "normal" sex hormones act on a genetically abnormal immune system or alter the expression of genetic susceptibility factors. The influence of gender and sex steroids on the immune response has been reviewed.[2] Women are known to have higher levels of immunoglobulins than men and a decreased cell-mediated immunity; natural killer (NK) cell activity is decreased during the peri-ovulatory period and interleukin-1 (IL-1) production is modified *in vitro* by estrogens and progesterone. The presence of cytoplasmic receptors for estrogens and androgens in lymphoid cells, or in the thymic matrix, may explain why these sex hormones are able to modify the function of these organs and to interact with the immune system and regulate it.

Prostaglandins could also mediate the effect of sex hormones on immunity. Progesterone acts on the endometrium, causing it to secrete mucus, vasoactive substances, and prostaglandins. Prostaglandins are known to have both pro- and anti-inflammatory effects through lipoxygenase and cyclo-oxygenase products, respectively.[73]

There is no indication that a gene on the X, or the Y, chromosome is involved in MS. Disease transmission is certainly not of a X-linked type and MS is not associated with other X-linked disorders. Linkage studies using probes for the X chromosome have been negative (GC Ebers, personal communication). Mitochondrial diseases are transmitted by affected mothers to children of both sexes. Affected MS mothers transmit the disease to their progeny more often than affected fathers do, but we have well documented examples of father-to-child transmission, thus discarding the possibility of a mitochondrial gene in the transmission of MS. Tourette's syndrome is a further example of a genetic disorder which, although reportedly attributable to a single autosomic dominant gene, is three times more frequent in men than in women.[74]

In conclusion, women have a definitely increased susceptibility to MS. This is clear in the gender distribution of global patient populations, and in familial studies as well. The number of twin pairs with known sex distribution, although small, indicate an increased concordance rate in women. We cannot offer a definitive explanation for these observations. Sex hormones, through their effect on the immune response, may be involved. Genetic factors could also be operative. Obviously, we will have to know more about the interaction of multiple genes, and non-genetic factors, in the acquisition of diseases which, like MS, are not monogenic disorders.

Acknowledgement

The authors wish to express their gratitude to Dr. G.C. Ebers for his support and helpful comments in the preparation of this manuscript.

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https://doi.org/10.1017/S0317167100041664 Published online by Cambridge University Press