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The Effect Of Sex on Multiple Sclerosis Risk And Disease Progression

Rhonda R. Voskuhl[1,*]

[1]Department of Neurology, 635 Charles E. Young Drive South, University of California, Los Angeles, Los Angeles, California 90095, U.S.A.

Abstract

Sex differences in the incidence or severity of disease characterize many autoimmune and neurodegenerative diseases. Multiple sclerosis (MS) is a complex disease with both autoimmune and neurodegenerative aspects and is characterized by sex differences in susceptibility and progression. Research in the study sex differences is a way to capitalize on a known clinical observation, mechanistically disentangle it at the laboratory bench, then translate basic research findings back to the clinic as a novel treatment trial tailored to optimally benefit each sex. This "Bedside to Bench to Bedside" approach based on sex differences in MS will be reviewed here, first for disease susceptibility then for disability progression.

Keywords

multiple sclerosis; sex differences; neuroimaging; neuroimmunology; neurodegeneration; experimental autoimmune encephalomyelitis

Sex differences in MS susceptibility.

There is a female preponderance to a variety of autoimmune diseases including MS, systemic lupus erythematosus, and rheumatoid arthritis(1). The female to male ratio in MS varies somewhat by geographic region from 2:1 to 3:1,(2) and has increased with time. This increase in the female to male ratio is driven by an increase in incidence for women, not by a decrease in incidence for men. Since the increased incidence in women has been observed over a period of decades, mechanisms involved may include gene-environment interactions or epigenetic factors.(3) One proposed factor is that pregnancy is protective in MS. Pregnancy decreases relapses in the third trimester and has longer term effects as shown by multiparity studies. More pregnancies, as compared to fewer, were associated with a decreased risk of first demyelinating event, and authors speculated that delayed or fewer pregnancies in recent decades could contribute to increased MS risk in women (4). This is not mutually exclusive of other possible environmental and social factors contributing to

[*]To whom correspondence should be addressed: Professor Rhonda Voskuhl, M.D., Department of Neurology, University of California, 635 Charles E. Young Drive South, Neuroscience Research Building 1, Los Angeles, CA 90095; rvoskuhl@mednet.ucla.edu; @rrvoskuhl; Phone (310) 206-4636, Fax (310) 206-7282.

Declaration of Conflicting Interest

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increased susceptibility of women to MS, including changes over the decades in smoking or work related stress in women, as examples.

Consistent with increased MS susceptibility in females, immune responses are more robust in healthy females compared to healthy males,(5, 6) including autoantigen specific responses in MS.(7) Sex differences in immunity have been shown across species,(5, 6) suggesting that basic biological differences between sexes are important since environmental and social factors are not conserved across species. Sex as a biologic variable includes the study of the role of differences in sex hormones and sex chromosomes on health and disease. The importance of the study of sex as a biologic variable has been emphasized by the National Institutes of Health (NIH) through its policy to include consideration of sex as a biologic variable in grant applications.(8)

Sex chromosome effects in MS susceptibility

All sexual dimorphism in mammalian biological systems ultimately arises from sex chromosomes, either directly from sex-linked transcriptional products or indirectly from circulating sex hormones produced after differentiation of female or male reproductive tissues. Regarding direct effects of sex chromosome genes, genome wide linkage analysis studies (GAWS) in MS have focused on autosomal genes that contribute to MS susceptibility, not on X or Y chromosomes. Females are XX and males are XY. Thus, XX versus XY differences include: 1) differences in X gene dosage, 2) maternal versus paternal X imprinting, and 3) Y gene presence or absence.(3)

The mammalian X and Y chromosomes are thought to have evolved from a pair of identical autosomes. One developed an allelic variation inducing testicular differentiation, which later became the Y chromosome, whereas the other became the X chromosome. The X and Y do not pair or recombine except for a terminal region known as the pseudoautosomal region (PAR). The non-PAR Y (NPY) follows a pattern of clonal inheritance from father to son that is subjected to heavy selection pressures. Over evolution, the Y chromosome has lost most of its initial genes and retained genes related to male reproduction. Today, the human Y chromosome contains only about 48 genes. In contrast, the X chromosome contains roughly 2000 genes or about 10% of the human genome. Based on the number of genes on the X chromosome that mediate functions other than reproduction, sex differences in MS susceptibility are more likely due to X, as compared to Y, gene effects. Indeed, many X chromosome genes are known to have immune functions, such as *Forkhead box p3 (Foxp3)* and *Toll-like receptor 7 (Tlr7)*. To influence disease susceptibility, sex chromosome gene effects do not require sequence variation as detected by GWAS studies of autosomal genes. Instead, they can influence susceptibility through sex chromosome dosage effects, resulting in differential expression of the same gene sequence.

Regarding X dosage, to ensure that most X chromosome genes are expressed at the same dose in females and males a mechanism called X-inactivation evolved to silence one of two non-PAR regions of X (NPX) in females. X inactivation is efficient across mammalian species. About 3% of genes escape X inactivation in mice, and about 15% in humans. Direct effects of sex chromosomes could be due to a differential dosage of X genes that escape

inactivation and are expressed higher in XX than XY. Regarding X dosage effects in patients with autoimmune diseases, the best studied is lupus. Lupus affects females more often than males with a ratio of 9:1. Notably, XXY males (Kleinfelter's syndrome) are more susceptible to lupus than XY males. This suggests that having two X chromosomes, as compared to one, increases disease susceptibility. However, this evidence is confounded by a difference in levels of sex hormones in Kleinfelter's individuals, both those at baseline and as treatments. It is difficult to separate out effects of sex chromosomes from effects of sex hormones in humans because sex chromosome differences are inherently tied to sex hormone differences. The XY genotype is associated with testes and the XX genotype with ovaries.

To study the effect of sex chromosomes, not confounded by a difference in sex hormones, Four Core Genotype (FCG) mice are used in preclinical models.(9) The *Sry* gene that encodes for testicular development is deleted from the Y chromosome (designated as XY-). Since they have no *Sry* gene, they are by default ovary bearing (gonadal females). Comparison of XX versus XY- gonadal females permits identification of the effect of differences in sex chromosomes without the confound of a difference in sex hormones.(10, 11) This is superior to gonadectomy (ovariectomy or castration) studies of female and male mice, because gonadectomized mice had different levels of sex hormones prior to gonadectomy which can exert organizational effects on the developing immune and central nervous systems. In contrast, XX and XY- FCG mice have the same type of sex hormones throughout development and adulthood. Another advantage of the FCG mice is that the *Sry* gene is added back at an autosomal location in XX *Sry* and XY- *Sry* mice. Since the *Sry* gene encodes for testicular development, XX *Sry* and XY- *Sry* mice both have testosterone. Together the FCG mice permit the study of differences in sex chromosomes in a female hormonal environment in XX versus XY- mice and in a male hormonal environment in XX *Sry* versus XY- *Sry* mice. This can ultimately be critical to identify gene-hormone interactions. We hypothesize that a sex chromosome gene product could have synergistic or antagonistic effects with the sex hormone for which it coevolved, depending on whether selection pressures favor shifting toward one direction versus achieving balance.

Our group used the FCG mice to study sex chromosome effects in the most widely used MS model, the classic CD4 T lymphocyte mediated autoimmune disease experimental autoimmune encephalomyelitis (EAE). Adoptive transfer of autoantigen-stimulated XX immune cells, compared to XY- cells, induced worse clinical disease scores and neuropathology, along with decreased Th2 anti-inflammatory cytokines IL-10 and IL-13.(11) These studies demonstrated a role for sex chromosomes in the induction phase of adoptive EAE. A more proinflammatory phenotype of XX compared to XY- mice was also demonstrated in experimental(11) and spontaneous(10) lupus models.

To identify a possible X gene dosage effect, we recently assessed CD4+ T lymphocytes for levels of expression of X genes known to escape X-inactivation.(12) The most differentially expressed X escapee with higher expression in females as compared to males in both humans and mice was *Kdm6a*. KDM6A regulates expression of many genes by encoding for a histone demethylase that removes repressive trimethylation on histone H3 lysine 27 (H3K27me3) to expose chromatin for transcription. Functional effects of KDM6A were

determined in EAE using targeted deletion of *Kdm6a* only in CD4+ T lymphocytes. Clinical EAE scores and neuropathology were less severe in conditional *Kdm6a* knockout (KO) mice compared to wild type (WT). To investigate downstream genes regulated by *Kdm6a*, whole transcriptome analyses of CD4+ T lymphocytes from conditional KO and WT mice with EAE were performed using RNA sequencing and canonical pathway analysis. The top upregulated gene pathway in CD4+ T lymphocytes of mice with a selective deletion of *Kdm6a* was the Th1 and Th2 Activation Pathway, and the second was the Th2 pathway, while the most downregulated was the Neuroinflammation Signaling Pathway. At the protein level, there was a shift toward Th2 cytokine production and from a memory to a naïve T cell phenotype with *Kdm6a* deletion. Together this demonstrated that the X escapee *Kdm6a* in CD4+ T lymphocytes is an important regulator of immune genes and has a disease promoting function in EAE. Expression of KDM6A from two alleles in women versus one allele in men may contribute to the higher susceptibility of women to MS, and modulation of *Kdm6a* in CD4+ T lymphocytes warrants investigation as a therapeutic target for MS.

Another sex chromosome difference between XX versus XY comparisons is parental imprinting of X genes that undergo X-inactivation. Genomic imprinting is an epigenetic process that involves methylation of DNA to achieve differential gene expression. Methylation of a gene's promoter generally silences it. Imprinting results in divergent patterns of gene expression, such as having a gene locus expressed exclusively from the maternal X chromosome (X_m) or from the paternal X chromosome (X_p). In XY males, all cells express the maternal X imprint (X_m), while in XX females, half of the cells express the maternal X imprint (X_m), and half express the paternal X imprint (X_p). Thus, differential imprinting of X chromosome genes can lead to differential expression of X genes in XX females versus XY males. Our group quantified DNA methylation in the *Foxp3* upstream enhancer region using bisulfite sequencing in CD4+ T lymphocytes from proteolipid protein (PLP) 139-151 autoantigen immunized SJL mice. More methylation of *Foxp3* was observed on the paternal X chromosome (X^p) than the maternal X chromosome (X^m).(13) Significant *Foxp3* gene suppression in (X^mX^p) as compared to (X^mY) is consistent with the observation by others of less *Foxp3* mediated immune regulation in XX females compared to XY males during EAE in SJL mice,(14) and with more robust immune responses in females across species.(5, 6)

The third sex chromosome difference between XX versus XY comparisons is due to the presence or absence of a Y gene. Y chromosome consomic mice showed that strain-specific Y chromosome genes can modulate immunity.(15) Whether this is due to strain-specific allelic variants of Y genes that confer susceptibility naturally or due to experimental disruption of the balance between Y and X gene homologues within a given strain is unknown.(16)

Sex hormone effects in MS susceptibility

An effect of sex chromosomes on MS susceptibility is not mutually exclusive of an effect of sex hormones. MS is more frequent after age 18, but pediatric onset MS is an active area of investigation. Both girls and boys are peri or post-pubertal at MS onset, with a sex ratio of approximately 2:1.(17) This is consistent with a gene-hormone interaction, but does not rule

out an effect of other biologic or environmental differences between pediatric versus adult ages. There is no consistent evidence that menstrual cycling women who undergo bilateral surgical ovariectomy have altered risk for MS onset, and oral contraceptive use showed inconsistent results.(18, 19) Effects of loss of sex hormones during menopause or andropause has not been rigorously studied, but since MS onset is usually before age 55, it is unlikely that menopause or andropause increases MS susceptibility. This does not rule out an effect of menopause or andropause on disability progression in established MS, as discussed below.

Sex differences in MS disability progression.

Consistent with the importance of sex as a biological variable,(8) sex differences occur in not only the immune system, but also in the brain.(20) Sex differences in the brain are observed across species from humans to mice.(21) Healthy male brains are on average larger than those of females, and there are regional differences in substructure volumes even when accounting for differences in brain size.(22) Beyond brain structure, there are many sex differences in brain at the cellular, molecular, and functional levels.

Neurodegenerative diseases show sex differences. Parkinson's Disease (PD) is male predominant.(23) Age matched groups show increased Alzheimer's disease (AD) risk in women.(24) However, men are at greater risk for mild cognitive impairment (MCI).(25) Loss of endogenous sex hormones in aging women and men are both associated with cognitive decline and increased AD risk.(26) This similarity between effects of menopause and andropause could be related to testosterone's conversion to estradiol in brain by aromatase, such that deleterious effects of waning levels of either estradiol or testosterone can be due to decreased ligation of estrogen receptors in brain. Sex differences in neurodegenerative diseases with aging could reflect the differential timing of menopause versus andropause, with the former being abrupt at ages 46-52 years and the later being very gradual starting at approximately age 30 years.

Decades ago landmark papers showed that one of the early predictors of worse disability in MS was male sex as shown by a shorter time between disease onset to reaching a given disability level in men compared to women.(27, 28) A large natural history study of over 5,000 relapse-onset MS patients then found that male sex was associated with a shorter time to, and a younger age for, conversion to SPMS.(29) An even larger registry-based international study across 25 countries including 14,453 patients revealed that male relapse-onset progressive patients accumulated disability faster than female relapse-onset progressive patients.(30) Finally, subcortical gray matter atrophy and cognitive deficits were reported to be worse in MS men compared to MS women.(31-33)

An enigma.

Immune activity is thought to contribute to neurodegeneration in MS. So if the incidence of disease is higher and peripheral immune responses are more robust in women, then why isn't disability progression worse in women? Instead, it is worse in men. We have

hypothesized that sex related factors in MS play different roles in the immune system versus the central nervous system.(3)

Sex chromosome effects in MS disability progression

X chromosome genes are expressed in the brain more than any autosome, and the X chromosome has a rich repository of genes vital to brain development. X chromosome abnormalities have been linked to aberrant neurological development in several X-linked diseases. The expanding catalog of 'X linked mental retardation' (XLMR) genes to over 100, indicates that an inordinate amount of the X chromosome is devoted to normal brain development.(34) A critical role for X genes in neurodevelopment and dysfunction is consistent with their potential role in neurodegenerative diseases.

While it is challenging in MS to show an effect of sex chromosomes in the CNS that is not confounded by effects of sex hormones, this can be done in the preclinical MS model EAE. Our group showed for the first time an effect of sex chromosomes in the CNS response to injury during EAE.(35) The FCG model was used to study sex differences due to sex chromosomes, not confounded by differences in sex hormones. Bone marrow chimeras were used to study sex chromosome effects in the CNS, not cofounded by differences in the immune system. EAE mice with XY- sex chromosome complement in the CNS, compared with XX, demonstrated worse EAE clinical disease severity with more neuropathology. This finding was consistent with males having worse neurodegeneration than females in MS. Identification of sex chromosome genes involved in neurodegeneration is needed.

Sex hormone effects in MS disability progression

MS women report that their pre-existing MS symptoms worsen prior to the menstrual period, when estradiol levels are low. Also, MS disabilities may worsen with menopause.(36) Retrospective studies of oral contraceptive use in MS women has not suggested an effect on disability, but doses and types of estrogen were not taken continuously or optimized for an effect on this outcome. In a Phase 2 prospective trial, oral contraceptives with estradiol at relatively "high", but not "low", dose showed an improvement in cognition as a secondary outcome when taken with Interferon-beta.(37) Estriol treatment in a Phase 2 multicenter trial showed a one third further reduction in MS relapses in estriol plus glatiramer acetate (GA) treated subjects compared to placebo plus GA. In addition, cognitive processing speed as measured by the Paced Auditory Serial Addition Test (PASAT) improved more in the estriol treated group than in the placebo treated group. Also, more cognitive improvement correlated with higher estriol blood levels(38). Finally, the cortical regions spared from atrophy in the estriol treated group compared to the placebo treated group involved the medial frontal cortex, a region implicated in problem solving and attention and previously shown to be activated on functional MRI during arithmetic strategy selection and counting.(39) Regarding neuroprotective mechanism, MS models have shown that neuroprotective effects of estradiol and estriol can occur through actions on estrogen receptor alpha on astrocytes and estrogen receptor beta on oligodendrocytes and CD11c+ myeloid dendritic cells.(40, 41) Together, this induces remyelination and enhances synaptic

plasticity. Further trials to assess estriol's neuroprotective effects in MS women are warranted.

Testosterone also has neuroprotective properties which can be mediated through its conversion to estrogen in the brain by aromatase as well as through direct effects on androgen receptors. Whether the gradual 1-2% reduction in blood testosterone level in men starting at age 30 years eventually contributes to worse MS disability later during andropause remains unknown. MS men with lower blood testosterone levels as compared to higher were found to have worse EDSS scores and performed more poorly on cognitive testing when followed longitudinally.(42) Our group treated ten MS men with daily testosterone (Androgel) in single arm crossover study to increase blood testosterone levels to the high normal range. Regional gray matter atrophy sparing was observed with one year of testosterone treatment.(43) Regarding neuroprotective mechanism, preclinical models of MS have shown that testosterone treatment induces remyelination and enhances synaptic plasticity.(44, 45) Further trials to assess testosterone's neuroprotective effects in MS men are warranted.

Conclusions

Sex differences have been shown in MS susceptibility and disability progression. These differences may be due to differences between women and men in sex chromosome gene expression in the immune system or the CNS and may be modified by sex hormones. Determining mechanisms underlying sex differences in MS can lead to novel treatments tailored for both women and men with MS.

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