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Review

Contributing factors in multiple sclerosis and the female sex bias

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ABSTRACT

Autoimmune diseases, such as multiple sclerosis (MS), show a higher incidence rate in women compared to men, which may be due to differences in the immune system, sex hormones, or both. Furthermore a disruption in homeostasis within these systems appears to be contributing to the etiology of MS. These systems are also influenced by the environment and metabolic factors necessitating the adoption of a broader viewpoint of the contributing factors in MS in the search for effective therapeutics.

1. Introduction

Autoimmune diseases result from a disruption in the normal defense mechanisms of the immune system leading to a failure of self-tolerance. Normally there are various checkpoints along the lymphocyte development pathways to prevent activation against the body's own tissues, but with an autoimmune disease, these become disrupted through unknown mechanisms leading to damage to a variety of organs and tissues. Recent research has demonstrated that approximately 5% of the population in developed countries suffer from an autoimmune disease and approximately 78% of the patients are women [1,2] leading researchers to believe that the factors contributing to sex differences may be tied to factors contributing to pathogenesis.

Multiple sclerosis (MS) is an autoimmune disease in which the interaction between hormones and the immune system plays a role in disease progression but the mechanisms by which this occurs are incompletely understood. In its earliest stages, MS presents as a disruption in self-tolerance of immune cells against the self-antigens of the myelin sheath, triggering the destruction of the myelin layer insulating the axons. This autoimmunity occurs with a state of chronic inflammation that prevents healing while also promoting the development of severe lesions that progress MS into a neurodegenerative state.

MS presents with a high degree of variability in afflicted individuals partly because the CNS is able to undergo some level of repair. This allows the alleviation of symptoms for some time until another bout of disease causes more damage. The back-and-forth of symptomatic and asymptomatic states is the relapsing-remitting form of MS (RRMS) which is characterized by acute attacks from which recovery can last for months. Another form of MS can be experienced with progressive symptoms that do not completely remit throughout the lifetime of the individual. Progressive MS can be primary, secondary or relapsing and is a gradual but steady progression of disability [3].

The heterogeneous nature of MS makes it a particularly difficult disease to manage. Current standards of medical practice involve the use of immunosuppressive and immune-modulating therapy which generally acts more as a symptom management protocol than a cure. Furthermore treatment routines seem to have only a delaying effect on disease progression while also being challenging to implement since each round of therapeutics has to be directed at a particular phase of the disease [4]. These challenges have sparked an interest in alternative methods of treatment, such as hormonal therapy to alter the female hormonal profile, which could also be indirectly immunomodulatory. Although these changes may be highly beneficial to some MS patients, much is still unknown about the factors contributing to MS which precludes the necessary shift

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in focus from therapy to prevention of disease. The possible factors contributing to the sex difference in MS are genetic, immune, and hormonal all of which can also be modulated by the environment and metabolic state. The aim of this paper is to report on the current understanding of MS in order to outline areas that could benefit from further research.

2. Genetics factors: Sex bias in MS

The contribution of X chromosomes in MS was explored through the experimental autoimmune encephalomyelitis (EAE) animal model commonly used in MS research. The researchers isolated the sex chromosome influence on EAE from the hormonal influence by deleting the testes-determining *Sry* gene from the Y-chromosome of the male mice. This led to the development of a female phenotype in XY^- mice. Both XX and XY^- mice express a female hormonal profile, therefore the researchers performed ovariectomies on both groups. With the induction of EAE they found that XX mice had a significantly higher susceptibility as well as a more severe disease progression, indicated by a higher degree of inflammation in the CNS. They also assessed castrated XX*Sry* and XY^-*Sry* mice expressing a male hormonal profile and found a similar bias of a female sex chromosome complement predisposing the subjects to the development of EAE. These results offer strong evidence that sex chromosomes have the potential to act independently of sex hormones in conferring disease susceptibility to females. Furthermore, these results were true only for the SJL mouse strain that has been demonstrated as having a female:male difference in EAE thus effectively modeling the sex-bias seen in humans [5].

The "Kast-Stewart hypothesis" implicates disturbances in the X chromosome inactivation process as conferring susceptibility to autoimmune disease [6,7]. X inactivation is the epigenetic silencing of one chromosome in the XX complement which confers a mosaic pattern of expression in each individual female [8]. The process is evolutionarily useful since it is responsible for gene dosage compensation between females and males and it seems to be a random process at the level of the entire organism. A layer of complexity is added to the process with X-inactivation being nonrandom, or skewed, for an area where the same cell types converge for a similar function. In these patches an X-chromosome from one parent shows preferential expression. Skewing in X chromosome inactivation has been observed in haemopoietic stem cells (HSCs) in the blood and bone marrow which give rise to the myeloid and lymphoid lineage of blood cells. The variation in patterns of expression can be constitutive or acquired with age [9] and the pattern has also been found to be heritable [10]. A breakdown in self-tolerance can be explained as a product of skewed inactivation since the differential expression of self-antigens could influence the immune system into action [11].

A study explored differential patterns of X inactivation in patients with MS by comparing 568 female patients with controls but a significant difference in degree of skewing towards one X chromosome's expression between the two groups was not found. Further comparison between the patients was conducted, grouping them according to the type of MS, RR-MS and progressive MS, and the researchers were able to demonstrate a significant difference in the level of skewing [12]. These findings suggest that the heterogeneity of MS is being expressed at the genetic level and perhaps grouping the various types of MS as different presentations of the same disease may not be accurate.

Other hypotheses for increased susceptibility of women to autoimmune diseases are the reactivation hypothesis and haploinsufficiency hypothesis [13] however a literature search relating to these did not reveal studies exploring the association of X chromosome reactivation and haploinsufficiency with disease preponderance in MS. Future research targeting this line of thought may be beneficial in elucidating further roles of the X chromosome in pathogenesis of MS.

3. The immune system in MS

3.1. The influence of sex on the immune system

Sex chromosome complement is also associated with differences in immune profiles created by cytokine release from various cell types. Females are more likely to develop a Th1 response except during pregnancy when a Th2 profile prevails. A Th1 response establishes a proinflammatory environment and a Th2 response promotes antibody (Ab) production [14]. This switch leads to a significant inhibition on the responsiveness of the immune system which is also associated with alleviation of MS symptoms.

The X chromosome influence on the immune profile is exemplified by the finding that ovariectomized XY^- female mice stimulated with autoantigen produce significantly higher levels of Th2 cytokines interleukin (IL) -13 and -5 compared to XX females in the EAE model of MS, with some evidence of higher IL-10 as well [5]. These cytokines have anti-inflammatory roles and contribute to a less severe clinical score of XY^- mice compared to XX. IL-13 may also have the ability to limit Th2 responses, further decreasing immune activation by decreasing cytokine secretion and Ab production [15]. IL-13 maps to the X chromosome as do the genes for IL-2Rγ chain and IL-9R (CD129) which promote lymphoid and myeloid cell development [16–19]. Research suggests that the levels of beneficial cytokines could be disrupted with EAE through an unknown mechanism thus reducing the body's ability to resist its onset. The connection of these cytokines to the sex chromosome complement is incompletely understood, but there is the possibility that the immune profile differences between XY^- and XX subjects are the result of the Y chromosome influence on immune factor expression. It has been thought for a while that the most significant contribution of the Y chromosome is the testes-determining factor but recent research has demonstrated that it has influence on immune function as well. Hypothetically speaking, an immune factor produced by genes on the Y chromosome but acting independently of sex holds the potential of becoming an administrable therapeutic. Therefore it is worthwhile to explore sex influences on MS without limiting the research to either sex thus allowing comparison between the two.

A capacity for regulation of autoimmunity has also been shown with the regulatory T cell. Naturally occurring CD4+ CD25+ regulatory T cells (nTregs) expressing an X-linked transcription factor, *FOXP3*, can directly suppress self-reactive T cells. In MS nTregs are upregulated in the CNS with a subsequent decrease in the periphery. As evidenced by the chronicity of MS, this migration is not sufficient in combating pathogenesis, possibly due to impaired functionality of the nTregs [20]. This functional deficit may be a lowered level of expressed FoxP3 protein [21] and upregulation of FoxP3 with stem cell therapy has been shown to ameliorate the symptoms of MS [22]. These findings support the involvement of Tregs and the expression of X-linked transcription factors in disease progression.

Other recently implicated immune factors conferring disease risk in a sex-biased manner are human leukocyte antigen (HLA) DR alleles expressing major histocompatibility complex (MHC) II molecules and the strongest genomic association of MS has been with the *HLA-DRB1*15* alleles on chromosome 6 [23–25]. MHC haplotypes show a significantly increased inheritance in a mother-to-daughter fashion and this finding could explain the development of MS as a product of transgenerational epigenetic effects [26].

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