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Review Article

Autoimmune Diseases and Their Prevalence in Females: A Review

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ABSTRACT

Autoimmune diseases affect approximately 8% of the population, 78% of which show female preponderance. The reasons for the high prevalence in women are unknown, but circumstantial evidence links autoimmune diseases with preceding infections. One of the most putative mechanisms is related to sex chromosomes, based upon the recent observation that women with autoimmune diseases manifest a higher rate of circulating leukocytes with a single X chromosomes leading to X Inactivation. One of the other factors are sex hormones. Sex hormones may further amplify this hyperimmune response to infection in susceptible persons, which leads to an increased prevalence of autoimmune disease in women.

Key words: Autoimmune diseases, female preponderance, X Chromosome inactivation

INTRODUCTION

Many decades ago scientists and clinicians alike observed that there were striking differences between the immune responsiveness of males and that of females. In general, females had superior humoral and cell-mediated immunity. Simultaneously, clinicians noted that women were more resistant to a variety of infections, which correlated with their greater longevity. Although these observations implicate the influence of sex-hormonal factors, these aspects received relatively scant attention. In subsequent years, when the concept of immunology advanced from a mere response to infectious agents to include a variety of complex situations such as loss of self-tolerance and aberrant responses to self-antigens (autoimmunity), it became apparent that women also had exaggerated responses to auto antigens and hence were much more susceptible to autoimmune diseases. [1] Autoimmune encompass nearly 70 distinct clinical entities. Among the earliest and most intriguing observations is the discrepancy in the prevalence of autoimmune disease between females and males. [2,3]

Any discussion of autoimmune disease requires a basic understanding of the function of the normal immune system, which, simply stated, is to fight infection and heal wounds. The components of that system are cellular and humoral. Immunity is frequently categorized as natural (nonspecific or innate) and acquired (specific). The primary cellular components of the nonspecific immune system are leukocytes (macrophages, eosinophils, basophils), which act by phagocytosis, whereas the primary cellular components of the specific immune system are lymphocytes, which can be further subcategorized into B cells and T cells. The function of the specific or acquired immune system is to distinguish between self and non-self. When confronted with an antigen

or foreign ‘‘invader,’’ B cells produce an antibody (immunoglobulin) specific to the foreign antigen. The B cell, once stimulated by an antigen, is programmed to ‘‘remember’’ that antigen in case it is detected again and mobilize the immune system if it does. T cells have antigen receptors on their cell surfaces and are even further subcategorized into helper and killer cells. There are two forms of T-cell receptors: those responsible for major histocompatibility complex restricted antigen recognition the αβ receptors and those that are nonrestricted the □ɣ receptors. Cytotoxic or killer T cells (□ɣ) attack antigens directly, whereas helper T cells (αβ) produce cytokines and stimulate B cells and leukocytes to attack antigens. [4]

Cytokines, such as interferon and interleukins, are immune factors involved in the inflammatory process. Helper T cells are implicated in autoimmune diseases because they mistake the body’s own cells (self) as antigen and then trigger responses to destroy it. Specific auto antibodies have been identified for several autoimmune diseases. The complement system, a cadre of more than 30 identified proteins, is also involved in regulating the immune response. The main function of complement is to clear immune complexes, which are essentially the cellular debris left after immune activity has occurred. A failure of the complement system can contribute to autoimmune disease manifestation by failure to regulate cellular apoptosis and the deposition of immune complexes, which leads to organ system damage. [4]

Autoimmune diseases are a group of disorders that involves the recognition of ‘‘self’’ as a foreign antigen and the production of auto antibodies that attack native cells as foreign. [6] The main differences which cause an increased predilection in females to develop autoimmune diseases can be broadly categorized into following etiological factors. The difference in the immune response between the two genders, Role of Sex Hormones, Genetic Susceptibility and History of Pregnancy.

ROLE OF IMMUNE RESPONSE

Distinct immune environments in males and females underlie many of the sex differences in autoimmunity. These environments are established by the cytokines released by immune cells, particularly T Helper (TH) lymphocytes. These cells respond to an immune challenge in one of two ways: TH1 lymphocytes secrete interleukin-2 (IL-2), interferon-y (IFN-y), and lymphotoxin, establishing a proinflammatory environment, whereas TH2 lymphocytes secrete IL-4, IL-5, IL-6, IL-10, and transforming growth factor-: (TGF-4), which promote antibody production. Both sets of lymphocytes exert cross-regulatory influences on each other. Females are more likely to develop a TH 1 response after challenge with an infectious agent or antigen, except during pregnancy when a TH2 environment prevails. (Figure 1) [5]

The degree of immune response also differs between men and women. Immune responses tend to be more vigorous in females, resulting in greater antibody production and increased cell-mediated immunity after immunization. Important questions remain about the differences between males and females in production and secretion of immunomodulatory mediators such as TGF-3, interferons, prostaglandins, and individual TH1 and TH2 cytokines. [5]

It is seen that females have higher immunoglobulin levels at baseline and produce more immunoglobulin in response to infection or immunization. [6-15] This difference first becomes apparent during puberty and persists only throughout the female reproductive years. [8-10] Interestingly, hypogonadal males with Klinefelter syndrome have immunoglobulin levels that are comparable to those of normal females, and with androgen administration, antibody levels diminish and

approximate quantities seen in healthy male subjects. [16]

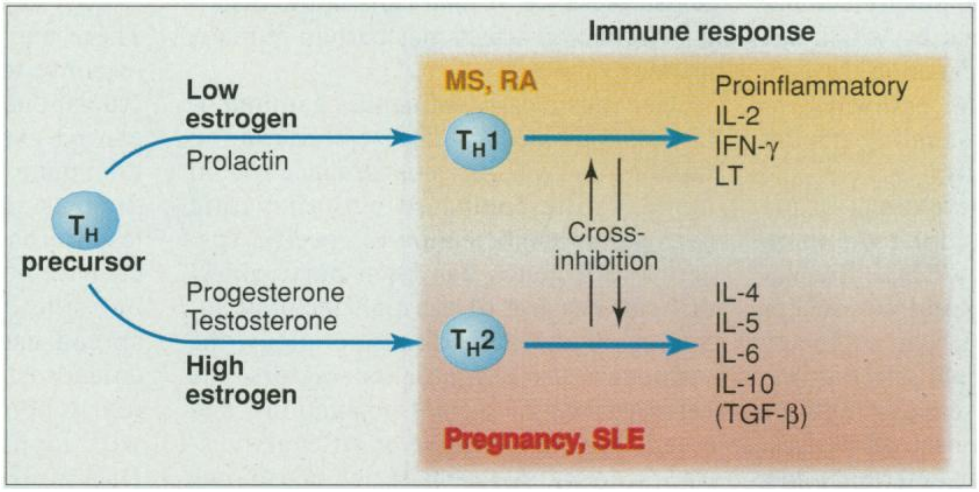

Figure 1

Role of Sex Hormones

Sexual dimorphism in immune response between men and women is directly linked with women producing more profound cellular and humoral immune reactions and being more susceptible to autoimmune diseases.

Investigation into the role of sex hormones in the human immune response has focused on differences in number and function of B cells and T cells. A comparison of the number and subsets of T cells in men versus women reveals a similar number of lymphocytes in each group, but the percentage of T cells is lower in men, which may be caused by increased testosterone concentrations. The differences in immune response between men and women and among women in different reproductive stages may be caused by the direct effects of sex hormones on cytokine production.

Estrogen may have an effect on B-cell subsets in that they seem to enhance the survival of autoreactive B cells and may play a role in the higher incidence of autoimmune diseases in women. Women also demonstrate higher levels of IgG and IgM than their male counterparts, which may be caused by a stimulating effect of female sex hormones or an inhibiting effect of testosterone. Estrogen increases antibody production, whereas testosterone decreases it. [6]

The acquired immune system of females differs from that of males, because estrogens stimulate immunologic processes driven by CD4 TH2 cells and B cells, whereas androgens enhance CD4 TH1 and CD8 cell activity. [9,17-21] Autoimmune diseases that are mediated by TH2-dominant lymphocyte activity are proportionately more female dominant than those conditions that are driven by TH1-dominant activity.

GENETIC SUSCEPTIBILITY

The role of sex chromosomes in autoimmune diseases has been widely studied in the past decade, first with the suggested model of fetal microchimerism, subsequently with X-inactivation patterns, and finally with X-chromosome monosomy and duplication. [22] In mammals, the female has two large, gene-rich X chromosomes, whereas the male has a single X chromosome and a Y chromosome, which harbours few genes. If the X-linked genes were expressed equally in both sexes, females would produce approximately twice the level of X linked gene products as would males. Since the great majority of genes on the X are not concerned with sex determination and reproduction, this difference would disturb metabolic balance in one sex or the other. In mammals and

some other groups with XY sex determination, a system has evolved to bring about the equivalence in expression of X-linked genes in females and males. In mammals, most of the genes on one of the Xs in the female are transcriptionally silenced in aprocess called X-chromosome inactivation (XCI), the focus of this entry. [23] X inactivation in somatic cells is generally random, with the maternal and paternal Xs having an equal probability of inactivation. [22] The difference in the process of X inactivation leads to an exaggerated immune response resulting in an increased predilection for females to develop autoimmune diseases.

HISTORY OF PREGNANCY

Fetal microchimerism was first suggested based on the observation that most autoimmune diseases have their peak of incidence following menopause. Indeed, maternal and fetal cells are exchanged during pregnancy, leading to fetal cell persistence (i.e. microchimerism) in the mother. Chimeric fetal cells are often hematopoietic and can differentiate into somatic cells in multiple organs, potentially acting as targets for autoimmunity and resembling graft versus- host disease after stem-cell transplantation. [24] Fetal cells persist in maternal circulation for years after birth, a state known as microchimerism. It has been recently proposed that these cells are involved in the initiation and postpartum flares of autoimmune disease, but exactly how microchimerism is involved in susceptibility to autoimmune disease, its initiation, and severity is not known. Moreover, it will be important to determine whether the continued presence of fetal cells in the maternal circulation affects postpartum immune responsiveness. [5]

SUMMARY

Autoimmunity is the result of a multifactorial process in which environmental triggers, genomic background, and other factors might well coexist and all be necessary in different magnitudes, although none is sufficient per se. While clinicians and scientists may be far from preventing or eradicating autoimmune disorders, this article has by enlarge encompassed all the major etiological factors which makes females more prone to develop autoimmune disorders. These factors could act as a single entity or may predispose their effect making the disease process worse. By finding out the etiological factor, it would make the diagnosticians easier to implement their therapeutic approach and the well being of the patient.

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