INTRODUCTION

The etiology of autoimmune diseases is still not clear but genetic, immunological, hormonal and environmental factors are considered to be important triggers. Most often autoimmunity is not followed by clinical symptoms unless an additional event such as an environmental factor favors an overt expression. Many environmental factors are known to affect the immune system and may play a role as triggers of the autoimmune mosaic Infections: bacterial, viral and parasitic infections are known to induce and exacerbate autoimmune diseases, mainly by the mechanism of molecular mimicry ***(Molina and Shoenfeld, 2005).***

This was studied for some syndromes as for the association between SLE and EBV infection, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection and more. Vaccines, in several reports were found to be temporally followed by a new onset of autoimmune diseases. The same mechanisms that act in infectious invasion of the host, apply equally to the host response to vaccination. It has been accepted for diphtheria and tetanus toxoid, polio and measles vaccines and GBS. Also this theory has been accepted for MMR vaccination and development of autoimmune thrombocytopenia, MS has been associated with HBV vaccination. Occupational and other chemical exposures are considered as triggers for autoimmunity. A debate still exists about the role of silicone

implants in induction of scleroderma like disease ***(Molina and Shoenfeld, 2005).***

Not only foreign chemicals and agents have been associated with induction of autoimmunity, but also an intrinsic hormonal exposure, such as estrogens. This might explain the sexual dimorphism in autoimmunity. Better understanding of these environmental risk factors will likely lead to explanation of the mechanisms of onset and progression of autoimmune diseases and may lead to effective preventive involvement in specific high-risk groups ***(Molina and Shoenfeld, 2005).*** So by diagnosing a new patient with autoimmune disease a wide anamnesis work should be done ***(Molina and Shoenfeld, 2005).***

It has long been recognized that environmental influences play an important role in the risk of developing chronic rheumatic disease. Defining specific pathogenic environmental mediators that may trigger the development or progression of autoimmune disease remains a focus of increasing investigative effort. Factors promoting disease may not be identical to factors that influence the severity or progression of the disorder. Human monozygotic twin studies, animal studies, and genetic models demonstrate that genetic influences strongly determine whether one will develop autoimmunity, however, genes affecting the metabolism of exogenous agents that may trigger disease expression have only recently drawn attention ***(Harel and Shofeld, 2006).***

Tobacco smoking has been linked to the development of rheumatic diseases, namely systemic lupus erythematosus and rheumatoid arthritis, and has been shown to interact with genetic factors to create a significant combined risk of disease. Smoking also affects both the course and the outcome of rheumatic diseases. Smoking increases the risk of dermatologic features and nephritis in systemic lupus erythematosus, rheumatoid nodules and multiple joint involvement in rheumatoid arthritis and digital ischemia in systemic sclerosis, as well as further increasing the risk of accelerated atherosclerosis in these diseases. Smoking is known to modulate the immune system through many mechanisms, including the induction of the inflammatory response, immune suppression, alteration of cytokine balance, induction of apoptosis, and DNA damage that results in the formation of anti-DNA antibodies. No sole mechanism, however, has been linked to any of the autoimmune illnesses which therefore complicates full comprehension of the 'smoking effect'. Further studies, perhaps using animal models, are needed to analyze the exact effect of smoking on each disease separately ***(Harel and Shofeld, 2006).***

AIM OF THE WORK

The aim of this work is to highlight the relation between environmental factors and rheumatic diseases.

Chapter 1

SEX DIFFERENCES IN AUTOIMMUNE RHEUMATIC DISEASES

Introduction:

Some human autoimmune rheumatic diseases affect more women than men, but disease severity does not differ between the sexes. Quantities of sex discrepancies differ among the autoimmune diseases. Female predominance occurs in thyroid diseases (Hashimoto's, Graves'), some rheumatic diseases (lupus, rheumatoid arthritis, scleroderma, Sjögren's), and some hepatic diseases (autoimmune hepatitis, primary biliary cirrhosis). Male predominance characterizes other rheumatic diseases (ankylosing spondylitis, Reiter syndrome, and vasculitis) and an immunologically driven nephritis (Goodpasture's syndrome). Other autoimmune diseases (juvenile-onset diabetes, infammatory bowel disease, and idiopathic thrombocytopenic purpura) are sex neutral. Some of the basic facts are disputed, however. Published female/male (F/M) ratios vary tenfold (from 10–50) for Hashimoto's disease, sevenfold for multiple sclerosis, fivefold for Goodpasture's disease, fourfold for scleroderma, and threefold for lupus (Table 1) ***(Ioannou and Isenberg, 2000)***.

Table (1): Sex ratios of autoimmune diseases

F/M ratio	Diseases
9:1	Sjögren Hashimoto Graves' Systemic lupus erythematosus
2-3:1	Myasthenia gravis Multiple sclerosis Rheumatoid arthritis
~ 1:1	Autoimmune hemolytic anemia Idiopathic thrombocytopenic purpura Type I diabetes Vitiligo Pemphigus
< 1: 1	Goodpasture Ankylosing spondylitis

Pathogenesis

Most sex-discrepant autoimmune human illnesses are equally severe in both sexes. In animal autoimmune disease, when F/M ratios are high, disease severity is as well. Many authors attribute sex discrepancy to sex hormones. This article supported by the Barbara Volcker Center for Women and Rheumatic Disease and the Mary Kirkland Center for Lupus Research ***(Ioannou and Isenberg, 2000).***

Attribution focuses on estrogen's effects on in vitro immunity, in vivo amelioration of experimental disease by female castration or worsening by male castration/estrogen supplement, or human case reports in which castration or pharmacologic intervention has altered the severity of a clinical

course. If immune response is inherently different between men and women, however, sex-discrepant responses to vaccination, infection, and immunomodulation should occur ***(Vermeire et al., 2003).***

A test of the hypothesis that hormones modulate immune response in vivo is to examine sexual dimorphism in the response to vaccination or infection. The few studies that do look at sex differences after vaccination show modestly higher antibody titers in women but no other sex differences in clinical protection by, or adverse reactions to, vaccination. Most studies find male and female responses identical, an exception being that arthritic reactions to rubella are more common in women. Viral and bacterial infections affect men and women equally. Therapeutically administered cytokines induce autoimmune rheumatic symptoms equally in men and women, but more women who receive the anti–tumor necrosis factor-a agent infliximab for Crohn's disease develop antinuclear antibodies. Although antibody titers tend to be higher in women, differences in clinically important immune response do not account for the high F/M ratios of rheumatic disease ***(Vermeire et al., 2003).***

In many ''experiments of nature'' environmental exposures induce autoimmune disease. More men take drugs that induce lupus; unlike idiopathic lupus, drug-induced lupus is male predominant; more men are exposed to silica inducers of scleroderma-like disease, also male predominant; more women

were exposed to the contaminated cooking oil that caused a scleroderma-like illness in Spain, which was female predominant. More women took contaminated L-tryptophan; the resulting epidemic of eosinophilia-myalgia syndrome was female predominant. In acute Lyme disease, boys are more often affected than girls because of their greater exposure in outdoor play to infected ticks; when incidence of chronic Lyme disease is adjusted for acute disease exposure, there is no sex discrepancy. In many experiments of nature, the main determinant of F/M ratios is rate of exposure ***(Arbuckle et al., 2003).***

Serologic lupus begins decades before the first symptoms appear. To identify a sex-discrepant environmental cause requires inquiry about exposure decades before first symptoms. Potential differences include exposures caused by different recreational experiences, processing infecting organisms caused by different routes of exposure (eg, menstruation and intercourse render women susceptible to infection in ways that men are not), vulnerable periods (eg, the high attack rate of malaria in the postpartum period is an example), and threshold differences in immune responses ***(Arbuckle et al., 2003).***

Judging from available clinical experience, sex hormones are at best weak explanations for high F/M ratios. Population studies on effects of hormone therapy show either no or small increases of incidence of rheumatoid arthritis and lupus in patients taking these drugs. Estrogen replacement therapy, oral contraceptives, and ovulation induction probably do not worsen

lupus. Although synoviocyte estrogen receptors may be target organs in rheumatoid arthritis, these receptors are present in synovium of patients with chronic Lyme disease and ankylosing spondylitis, which are not female predominant. Androgens have no apparent role in the male predominance of ankylosing spondylitis ***(Petri et al., 2005).***

The effect of pregnancy on autoimmune disease is variable. Rheumatoid arthritis and multiple sclerosis remit during pregnancy. Lupus does not or only slightly worsens during pregnancy. Ankylosing spondylitis worsens. Pregnancy changes in disease severity can be caused by placental or maternal hormone, increased circulation, increased fluid volume, metabolic rate, hemodilution, circulating fetal cells, or other factors. A threshold mechanism could explain an increase in incidence without a corresponding increase in severity. An animal model suggests this possibility: estrogen may permissively allow survival of forbidden autoimmune clones ***(Petri et al., 2005).***

Hormones might influence F/M ratios by affecting nonimmune cells; for instance, hormone effects on endothelium might be critical for disease initiation. An unknown sex difference related to ovulation or menstruation cytokines, vascular rheology, or a biologic clock might be responsible for different disease experiences of the two sexes. In some mouse strains, healing is sexually dimorphic, the dimorphism being under estrogen control. At the single-cell level, male and female cells in culture are strikingly different ***(Heber-Katz et al., 2004).***

Evidence for genetic control of autoimmunity is strong for spondyloarthropathy, rheumatoid arthritis, and lupus. Sex-discrepant human leukocyte antigen–associated effects and genes on X and Y chromosomes are possible causes of sex discrepancy. Although ankylosing spondylitis has no X-chromosome susceptibility locus, CD40 ligand, some interferon-related genes, and other immunologically relevant genes are on the X or Y chromosome. Evidence that supports or refutes a chromosomal explanation for sex discrepancy is as follows: Susceptibility to lupus resides on the Y chromosome in the male-predominant BXSB mouse model. Differences in imprinting or differential X-inactivation have been sought but not found. Skewed X-inactivation in the thymus may lead to inadequate thymic deletion and loss of T-cell tolerance ***(Heber-Katz et al., 2004).*** Sex dimorphism of T-cell trafficking may be caused by sex-determined cell surface markers. Sex chromosomal differences are possible reasons for the sex discrepancy of autoimmune disease ***(Heber-Katz et al., 2004).***

Although the (NZB xNZW) F1 mouse model of lupus shows high female incidence and severity, the MRL lpr/lpr model is sex neutral and the BXSB model is male predominant. Castration/replacement experiments in (NZB x NZW) F1 mice demonstrate estrogen enhancement and testosterone suppression of spontaneous disease severity and incidence. Like its human counterpart, lupus in mice develops in young adulthood, which implies that incubation, maturation, or cumulative damage is required for disease expression ***(Hoyle et al., 2000).***

Male and female mice in germ-free environments are equally affected by lupus, but germ-free female mice develop higher autoantibody levels. Germ-free, antigen-free animals have less frequent disease than do germ-free or conventionally raised animals, which indicates environmental contribution to illness and leaves open the possibility that differential exposure causes sex discrepancy in humans. The p21 knockout and the DNAse 1 knock outmouse lupus models show slightly higher autoantibody levels in female mice. Inexplicably, glomerulonephritis is much worse in female p21 knockout mice but equals that of male mice in DNAse 1 knockouts. The human leukocyte antigen B27 gene transgenically expressed in rats induces a phenotype with features of psoriasis and ankylosing spondylitis. In a germ-free environment, the spondylitis does not occur. Introduction of specific gastrointestinal pathogens to the germfree animal induces spondylitis. Male predominance is true of this model, as it is of the human disease, but the reasons are unknown. In these animal models of autoimmune disease, genetic, hormone, life stage, and environmental factors are all relevant to disease causation. No consistent cause for sex discrepancy appears ***(Chitnis et al., 2000)***.

Men and women differ in ways that are not easily explained by hormones, chromosomes, or specific genes, such as body size and the monthly (chronobiologic) cycle in women. Most female predominant diseases cluster in the young-adult years, whereas autoimmune diseases that affect younger or older patients are more evenly divided between the sexes.

Characteristics of young adulthood that may explain female predominance include mode of sexual intercourse, pregnancy, chronobiology, non- hormonal effects of menstrual cycles, vascular responses, and as-yet unknown other variables. The large quantity and long duration of circulating fetal cells in scleroderma and other autoimmune disease patients and the finding of pregnancy-created chimerism in sites of autoimmune disease suggest a profound new biologic difference between men and women, the implications of which are unknown. ***(Chitnis et al., 2000)***

Explanations for sex discrepancy

In non-autoimmune human illnesses, the most striking differences of incidence occur when exposures to infectious agents or toxins differ between the sexes. If infections or toxins induce autoimmune disease, differences in exposure (perhaps decades before onset of clinical illness) remain as plausible explanations for the sex differences. If gonadal hormones play a role, they likely do so through a threshold or permissive mechanism rather than through immunomodulation. Differences related to X-inactivation, imprinting, X or Y chromosome genetic modulators, and intrauterine influences remain as alternate, theoretical explanations for sex differences of incidence. The epidemiology of some autoimmune diseasesd young, females suggests that an explanation for female predominance lies in exposure, vulnerable periods, or

thresholds rather than in the immune response itself. These topics remain to be explored. ***(Balomenos et al.,2000)*.**

Chapter 2

INFECTIONS AND RHEUMATIC DISEASES

The seasonal onset and geographic clustering of some rheumatic diseases has suggested a possible role for infectious agents as triggers of disease. There are many descriptions in the literature of individual patients with rheumatic diseases that are suspected to have been caused by a microbe, but epidemiologic evidence for the role of specific infections in rheumatic diseases is relatively sparse. The evidence offered is generally the presence of a serologic response, recovery of an organism or identification of part of the amplified genome of a microbe; however, many studies did not include appropriate control populations. No infectious agent that has been identified consistently induces any rheumatic illness in a specific population. Hepatitis B, for example, is known to be associated with polyarteritis nodosa in only 1–5% of 20 infected individuals ***(Mackay, 2005).***

Several appropriately controlled studies suggest an increased risk of RA and SLE after measuring the presence of antibodies to various viral components of the Epstein–Barr virus (EBV), cytomegalovirus, or and human herpesvirus in patients' sera, or using questionnaires and interviews to gather information from patients. Some of the

strongest evidence for infectious associations with rheumatic diseases come from studies of EBV. This ubiquitous virus has been implicated in numerous illnesses. The evidence that suggests EBV is associated with rheumatic diseases includes an increased presence of antibodies to viral peptides and the ability to amplify EBV genomes by polymerase chain reaction (PCR) in more patients with rheumatic disease than controls. Their increased knowledge of EBV and genes encoding auto antigens has strengthened the evidence for an association between EBV and SLE ***(Mackay, 2005).***

Parvovirus is well known for inducing reactive polyarthritis that spontaneously resolves in most cases, but several investigations have suggested parvovirus might be an etiologic agent in RA. In addition, in a study of children with an acute onset of arthritis, those with IgM antibodies to parvovirus B19 developed a chronic arthritis in distinguishable from juvenile RA, whereas those who lacked IgM antibodies to parvovirus B19 did not progress to a chronic form of RA. In a carefully conducted study, however Mamyrova et al. did not find an association between serum IgG antibodies to parvovirus B19 and juvenile dermatomyositis. The ‘hygiene hypothesis’ posits that the increase in the prevalence of immune-mediated diseases in developed countries might be related to an early-life environment that is relatively deficient in microbial flora. This hypothesis predicts that some types of