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Introductory Chapter: Systemic Lupus Erythematosus - Different Predisposing Factors

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1. Introduction

Systemic lupus erythematosus (SLE) is a complex, multisystem autoimmune disease characterized by impaired immune tolerance resulting in the production of pathogenic autoantibodies and immune complexes [1]. Prevalence of SLE ranges between 20 and 150/100,000 and its incidence ranges between 1 and 10/100,000 [2]. American College of Rheumatology revised their criteria for the classification of SLE [3]. Their incidence is most common in some ethnic group such as Asians, Australian Aborigines, African Americans, and Hispanics. Incidence rate has been raised in recent years that may probably due to better detection techniques for the disease. In the past few decades, the prognosis for SLE patients has been improved, and it was found that about 90% of the cases have 10-year survival rate [4]. This might be due to the fact that a combination of diagnosis of earlier disease and of milder disease and partially due to the development of various serological test used for SLE and combined used of steroids and various immunosuppressive drugs and availability of the techniques such as renal dialysis and transplantation [5]. Although, the exact cause of SLE remains elusive, but there is a consensus that it might be due to the combination various factors such as immunological, genetic and environmental. All these factors may somehow responsible for the chronic course of the disease. It is found that autoreactive T cells hold responsible for the activation of B cells that might be stimulated to produce antibodies by high levels of cytokines (pro-inflammatory) such as interleukin 10, interleukin 6, tumor necrosis factor- α and interferon γ in different SLE patients [6]. In addition, production of antibody might be elevated further by B and T cells through interaction via co-stimulatory molecules that inhibit apoptosis. Autoantibodies produce from these cells are very likely responsible for the pathogenic effect on tissues in different SLE patients [7]. In addition, impaired production of IL-10 and IL-12 causing B cell

activation and inhibition in the normal function of T cells [8]. Interleukin 12 responsible for the down-regulation of interleukin 10 and lower level somehow correlate with elevated activity and nephritis [9]. More recently, it has been assumed that the stimulus of autoantibodies production is the inability to dispose apoptotic cells from the body [10].

2. Different factors predisposing to SLE

SLE is an autoimmune disease which involves multisystem disorder whose etiology is unknown but supposes to be multifactorial in origin. Different epidemiological data showed that there are many factors that might trigger SLE. These include gender, age, racial, hormonal, genetic, and environmental factors.

2.1. Hormonal factors

The incidence and prevalence of SLE varies considerably worldwide [11]. In addition, gender discrepancies are also observed in SLE burden, with a higher number of cases was found in women as compared to men. It has been observed that this disease has been affected to about 80–90% women of all the reported cases [12]. Prevalence of SLE is far more in women in comparison to men [13]. In addition, if we compare female to male ratio during childhood, it was found to about 12:1 [14]. These data showed that hormone plays an important role in etiology of SLE [15]. Hormones such as estrogen have both anti-inflammatory and pro-inflammatory properties depending upon different influencing factors [16]. There are various studies that can explain the role of estrogen and its metabolites in SLE [15, 17]. The 2-hydroxyestrogens was found to be 10 times lower in patients with SLE than the control subjects, and the ratio of 16-hydroxyestrone/2-hydroxyestrogen was found to be 20 times higher in these SLE patients [18]. Previous studies also showed that SLE patients have increased the concentration of serum 16-hydroxyestrone. α -Hydroxylation of estrogen was found to increased in SLE patients, producing more estrogen metabolites that were reported to elevate B cell differentiation and activation of T cells [19]. Another important mechanism through which estrogen plays a role in SLE etiopathogenesis is the involvement of quinone-semiquinone redox cycling of estrogen to produce free radicals that can damage DNA. This would probably alter its antigenicity leading to the induction and increased level of SLE autoantibodies that somehow cross-reacting with native DNA [20].

Estrogens are known to have higher immune reactivity in females and are also contribute to triggering autoimmune diseases including SLE [14]. Various conditions (physiological, therapeutic, and pathological) such as menstrual cycle, inflammatory cytokines, chronic stress, treatment with a corticosteroid, oral contraceptives, and steroid hormone replacement might cause variation in serum estrogen concentration and this variation in concentration contribute to SLE in different groups of the population [21].

2.2. Genetic factors

The difference (polymorphism) in various types of genes may also enhance the risk for the development of SLE, and in most of the cases, different genetic factors are thought to contribute

to the pathogenesis of this disease. In most of the cases, SLE is caused by a mutation in multiple genes and rarely seen by a mutation in the single gene. Multiple genes, that are causing SLE, are linked to the function of the immune system and difference in this most likely effect proper controls and targeting of the immune system. Genetic factors along with environmental factors play an important role in the determination of SLE susceptibility [22]. It is suggested that genetic factors play an important role not only in disease susceptibility but also in the development of SLE phenotype [22]. The genes that can increase SLE susceptibility are the genes included in the interferon pathway, also containing IRF5, IF1H1, and STAT4 [23]. The biggest genetic risk for SLE is confirmed by deficiencies of complement pathway proteins such as C1q, B and C4A, and C2. Mutation in TREX1 gene causing the accumulation of DNA that encodes for 3' repair endonuclease activity. The defect in these genes is although rare but susceptibility in most patients arises from a combination of normal variation in different genes. High-density SNP screening of the major histocompatibility complex in SLE showed strong evidence for independent susceptibility regions including HLADR2, HLADR3, and HLA-DRB1 [24]. There are other types of genes that can regulate the immune system, are also implicated in SLE. These genes include those that can influence the function or survival of T and B lymphocytes (BANK-1, PTPN22, OX4OL, BLK, LYN, PD-1) or those involved in the clearance of immune complex including Fc γ RIIa, ITGAM, and complement proteins. The class II alleles HLA-DR2 and HLA-DR3 were found to be the most prominent genetic risk factors for SLE in some group (Caucasian group) and these alleles showed twofold to threefold increased the risk for this disease [25]. There are two alleles namely HLA-DQ and -DR, which interestingly showed a close association with SLE autoantibodies [26]. The signal transducer and activator of transcription (STAT4) genes were first identified in rheumatoid arthritis and later on, it shows strong association with SLE [27]. Careful analyses of this gene revealed that there is a strong association of this gene not only with SLE nephritis but also with double-stranded DNA, autoantibodies and younger age of onset [28]. The difference in the promoter of certain genes (pentraxin C-reactive protein, CRP) has been linked with SLE or SLE nephritis in some ethnic group [29]. CRP is an important candidate for SLE susceptibility. This protein is found to be an effective innate immune modulator that brings out the clearance of cell debris and apoptotic bodies and we know that any defect in the clearance of apoptotic waste is belief to be an important process that mainly responsible for the promotion and development of autoantibodies in SLE patients [29]. From all these studies, it is observed that genetic factors play an important role in SLE pathogenesis. These evidence suggest that these factors play a role not only in disease susceptibility but also in the development of disease phenotype.

2.3. Environmental factors

Although hormonal and genetic factors predispose towards SLE but the initiation of the disease may trigger from various environmental and exogenous factors. Different environmental toxicants and agents, such as alcohol, smoking, various chemical, ultraviolet light, various infectious agents, hormone, and therapeutic agents, have been involving in inducing SLE. All these environmental agents along with other types of factors have been associated with the occurrence of SLE [30]. Infectious agents may disturb immune regulation and stimulate various immune response through molecular mimicry; food influence the production of inflammatory mediators; drug or toxin alter cellular responsiveness and antigenicity of self-antigen;

and different chemical and physical agents like ultraviolet light, alcohol, etc. induce inflammation, causes cellular apoptosis, and also damage tissue and DNA. Various types of drugs like procainamide and hydralazine (aromatic amines or hydrazines) induce lupus-like symptoms in those individuals who are ingested or in contact with these agents [31, 32]. In addition, more use of hair dyes, which consists of aromatic amines, have been associated with the development of SLE [33]. Sunlight exposure is one of the main environmental factors associated with the induction and exacerbation of SLE. Exposure of ultraviolet light is found to be an important factor that may trigger SLE in many patients. This exposure of skin with ultraviolet light alter the position and structure of DNA as well as Ro and nRNP antigen and somehow increase its immunogenicity [34]. Several dietary factors along with various infectious agents are involved in the pathogenesis of SLE. There are the reports that showed that ingestion of alfalfa sprouts that consists of L-canavanine, might involved in the development of lupus-like syndrome [35]. The use of environmental estrogen had been increasing over the years and they are present in the human body from the consumption of meat and milk product from lives stock that is given synthetic estrogen [36]. Moreover, these estrogens have also been used by postmenopausal women and for contraceptive purposes. Hormone replace therapy as well as oral contraceptives has been shown to be a risk factor in the development of SLE [37]. The environmental estrogen with another endocrine hormone may act as an important agent to trigger autoimmunity in susceptible individuals. The development of SLE may depend on several factors such as genetic background, dose, sex, age, a period of exposure, and status of the immune system at the time of contact of these environmental agents.

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