MODELING OF IMMUNOSENESCENCE WITH AGING IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting multiple systems and presenting with a wide range of clinical symptoms. Disease phenotype alters from childhood to old age. The possible reasons for these differences are genetic factors, changes in the hormonal status, and the aging immune system. As a result of the disease itself or as a side effect of medications, SLE patients often experience manifestations associated with aging like cardiovascular disease and infection susceptibility. Furthermore, immunosenescence, which commonly affects the elderly subjects, may result from the continued immune system activation during the natural history of SLE. In this study, we aimed to analyze the immunosenescence in SLE, the differences and similarities in SLE phenotype at different age groups, and possible reasons for these changes.

Keywords: systemic lupus erythematosus; late-onset systemic lupus erythematosus; aging; immunosenescence; inflamming.


Introduction

Systemic lupus erythematosus (SLE) is the prototype of systemic autoimmune diseases. The presence of autoantibodies is an important characteristic of the disease. The development of the disease is influenced by numerous variables including genetic, immunologic, environmental (UV light exposure, infections, medicines), and hormonal conditions [1]. SLE is much more frequent among women than men. It affects women, especially between puberty and menopause [2]. Between puberty and menopause, the female/male ratio is around 9/1, although some studies have found it to be as high as 15/1 [3, 4]. Incidence rates range from 0.3 to 3.1.5 per 100,000 persons per year and have increased over the past 40 years, probably due to the detection of milder cases. Worldwide adjusted prevalence is around 50-100 per 100,000 adults [5].

In children, the incidence and prevalence are 0.36-2.5/100,000 and 1.89-34.1/100,000 children, respectively [6].

SLE affects multiple tissues and organs like joints, skin, kidneys, and cardiovascular, hematological and central nervous systems. The clinical findings are very diverse and the severity of the disease is highly variable [7, 8]. SLE is diagnosed clinically, with laboratory evidence of immunological reactivity or inflammation in several organs supporting the diagnosis. The aim of SLE treatment includes reducing symptoms and signs, controlling disease activity, minimizing adverse effects of drugs, preventing long-term damage, and improving health-related quality of life. Pharmacological therapy focuses on immunomodulation and immunosuppression, and specific treatments are individualized according to the disease’s manifestations and severity.
Some features like age, gender, ethnicity, and involved organs affect the prognosis of SLE. Major organ involvements, particularly the central nervous system and renal diseases, are considered poor prognostic factors [9].

The phenotype of SLE differs according to the age at symptom onset. Patients with childhood-onset SLE present with a higher prevalence of multiorgan involvement such as nephritis, neuropsychiatric manifestations, and hematological features and moreover, a more aggressive disease course with increased morbidity and mortality rates than patients with adult-onset SLE [10, 11]. By contrast, the prevalence of constitutional and mucocutaneous manifestations, hypocomplementemia and serositis in late-onset SLE patients (over 50 years old) is lower than in patients with childhood- and adult-onset SLE [12]. The possible reasons for these differences are changes in the hormonal status and immune system with age.

Many manifestations associated with aging, such as cardiovascular diseases or greater susceptibility to infections, can be found in SLE patients, either as a consequence of the disease or as a side effect of medication [13, 14]. Also immunosenescence, which often exclusively affects elderly subjects, might result from the continued process of chronic immunological activation and pro-inflammatory phenotypes during the natural disease course in SLE [15].

In this study, we aimed to analyze the immunosenescence in SLE, the differences and similarities in SLE phenotype in different age groups, and possible reasons for these changes.

Search Strategy

The PubMed database was screened according to the published guidance on narrative reviews [16] by using the following keywords: ‘aging’, ‘immunosenescence’, ‘systemic lupus erythematosus’, ‘juvenile SLE’, ‘early-onset SLE’, ‘late-onset SLE’. Review articles and original articles were selected for the study, while case reports were excluded. The search was restricted to English articles. Priority was given to the articles published during the last decade.

Aging versus “inflammaging” in SLE

The immune system goes through several changes while the individual is aging. Both innate and adaptive immune systems are affected during this process. Immunosenescence and inflammaging are two important concepts in this period. Immunosenescence refers to the shortcoming of immunological defenses and also losing self-tolerance. Thus, it causes increased susceptibility to infections, a decrease in vaccine effectiveness as well as an increase in the prevalence of cancer and autoimmune diseases. On the other hand, defective clearance of senescent cells can promote chronic low-grade inflammation. This phenotype is named ‘inflammaging’. It is characterized by a chronic low-grade pro-inflammatory state with raised levels of acute phase reactants, pro-inflammatory cytokines, and clotting factors over time [17-19].

The biological hallmarks of aging can be observed chronologically earlier in subjects with SLE. Moreover, the typical mechanisms associated with aging can be observed even in young SLE patients. In SLE, manifestations of aging are often seen within the heterogeneous clinical spectrum, either as a consequence of the disease course or as a result of treatment. The main mechanism of inflammaging in SLE is oxidative stress. Oxidative stress leads to inflammaging in different ways such as cell function impairment by oxidative damage to the intracellular biomolecules, promotion of cell apoptosis by excessive production of oxidized molecules and lastly neoantigen formation induction by modification of self-antigens. Overproduction of reactive oxygen species due to mitochondrial dysfunction causes T-cell activation, which is characteristic for SLE.

The similarities between the aging process and immune aging in SLE can be at clinical/macroscopic, cellular/microscopic, and molecular levels. Increased susceptibility to infections, decreased antibodies after vaccinations, and an increased prevalence of cardiovascular disease and cancer are among clinical similarities [20-22]. The molecular and cellular common hallmarks include genomic instability, epigenetic changes, attrition of telomeres, loss of proteostasis, mitochondrial dysfunction, deregulation of nutrient sensing, cellular senescence, exhaustion of stem cells, and intercellular communication [23]. Similarities in the innate immune system changes include low-grade inflammation (inflammaging), impaired phagocytosis, decrease in natural killer (NK) cell function and monocyte HLA-DR expression. In the adaptive immune system, an increase in memory T cells and CD28 negative T cells, and a decrease in naive T cells and interleukin-2 (IL-2) production by T-cells are observed both during aging and in SLE [8].

SLE phenotypes in different age groups

SLE manifestations differ with age. SLE can be
divided into three main groups according to age at diagnosis. Patients who developed SLE before the 18th birthday are classified with juvenile SLE (JSLE), those who experience disease onset between the ages of 19 and 50 are classified as having adult SLE (ASLE) and lastly, the patients diagnosed with SLE after the age of 50 are classified with late SLE (LSLE) [24]. There may be a distinct group in JSLE named as early-onset SLE with disease onset before 5 years of age. It is also called familial SLE and/or syndromic SLE, and monogenic factors play a role in pathogenesis. 15-20% of patients are diagnosed with SLE prior to adulthood and according to published data, 2-20% of the patients present after the age of 50 years [24, 25]. The ratio of females to males falls among younger and older age groups: 6:1 in JSLE, 13:1 in ASLE, and it falls to 3:1 in patients diagnosed ≥60 years of age [25] (Figure 1). In our cohort of pediatric SLE (n=262), the F/M ratio was even lower as 4.2:1 [26].

Late-onset SLE displays a milder phenotype than JSLE. Clinical manifestations that are more frequently seen in LSLE are (secondary) Sjögren’s syndrome, serositis and arthritis; while skin disease and nephritis are more commonly seen in JSLE [27, 28]. In a study by Hoffman et al. the prevalence of cutaneous symptoms such as generalized erythema, subacute cutaneous lupus, and chilblains, fever, renal involvement, encephalopathy, hemolytic anemia were higher in JSLE patients than in ASLE patients; whereas patients developed sicca symptoms and arthralgia less [29].

In a study by Tomic-Lucic et al. the LSLE group developed photosensitivity, and neuropsychiatric disease less frequently [30]. Choi et al. evaluated 201 SLE patients, and found that photosensitivity, oral ulcers, renal involvement, hematological signs such as anemia and thrombocytopenia (no difference in lymphopenia) and fever were significantly more frequent in JSLE than ASLE and LSLE [24]. It is noteworthy that renal involvement was least prevalent in LSLE group, whereas Sjögren’s syndrome and hypertension were more common in LSLE patients than the other two groups.

The frequency of autoantibody positivities and laboratory features also alter in different age groups. Anti-double-stranded DNA (anti-dsDNA) antibodies are seen most frequently in JSLE group and least in the LSLE group. Anti-smooth muscle (anti-Sm) and antinucleosome antibodies are also found more frequently in JSLE patients. More prevalent renal involvement in JSLE group is thought to be associated with anti-nucleosome antibodies and anti-dsDNA. In JSLE, complement levels, including C3, C4, and CH50 are more frequently decreased compared to LSLE patients. Although Sjögren’s syndrome is more prevalent in the LSLE group, there is no difference in the rate of anti-Ro/SS-A and anti-La/SS-B positivities between the groups [24]. Amaral et al. did not find any difference regarding anti-dsDNA profiles of adolescent and ASLE patients [31]. Hoffman et al. showed higher titers of anti-ribosomal, anti-dsDNA and anti-histone antibodies in JSLE patients [29].

Figure. 1. Female-to-male ratios in systemic lupus erythematosus (SLE) among different age groups (JSLE, juvenile SLE; ASLE, adult-onset SLE; LSLE, late-onset [≥60 years of age] SLE)
Renal involvement had a positive correlation with anti-dsDNA antibodies and a negative correlation with anti-ribosomal P [29]. But some studies showed that both antibodies are positively correlated with renal signs [32].

Another aspect affected by the age at onset is disease severity in SLE. The disease course is more indolent in the LSLE group than in the ASLE group, as reflected in the lower SLE disease activity index (SLEDAI) values and the less frequent use of corticosteroids and other immunosuppressive drugs [33, 34]. Medication use (glucocorticoids, mycophenolate, azathioprine, and cyclophosphamide) is more frequent in the ASLE group than the LSLE group, as well [35]. Juvenile-onset SLE patients have more active disease according to SLEDAI-2K measurement compared to other groups. Thus, close follow-up and more aggressive treatment are required for JSLE patients [24].

Juvenile-onset SLE patients have the highest risk of mortality, possibly due to the severity and longer duration of the disease. Mortality is higher among LSLE group compared to ASLE [36]. Higher mortality in LSLE could be related to increased age and prevalence of comorbid conditions [37].

Late-onset SLE patients have a higher frequency of osteoporosis, hypertension, type 2 diabetes mellitus, stroke, heart failure and liver cirrhosis [36, 38]. Also, treatment-related complications are more common in this group causing a need for a special clinical care [30, 39].

**Why does SLE phenotype differ according to the age at onset?**

SLE onset is most prevalent in females in child-bearing years. Although female predominance is seen in all age groups of SLE; there is a decrease in prepubertal and postmenopausal periods probably due to the hormonal milieu. This may be attributed to declining estrogen levels in addition to genetic and environmental factors [40]. SLE patients experience less common classical clinical manifestations and less active disease with lower estrogen levels [41]. According to several studies, postmenopausal onset was considered to be related to lower number of flares and lower SLEDAI score [42, 43]. In a SLE mouse model, delay in SLE onset and low levels of autoantibody titers were seen in ovariectomized female mice compared to the female mice group [44]. Estrogens have an impact on inflammation mostly mediated by estrogen receptor-alpha (ER-α) and ER-beta (β).

In animal models, ER-α had a pro-inflammatory effect and contributed to disease progression, while ER-β had an anti-inflammatory and immunosuppressive effect in lupus mice [45, 46]. In contrast to this information, Urowitz et al. suggested that postmenopausal women’s lower disease activity was due to shorter disease duration rather than hormonal changes [47].

The SLE disease mechanisms change with age. Although SLE pathogenesis is multifactorial and polygenic, genetic factors play a significant role, particularly in cases of familial early-onset SLE [48, 49]. There are a number of pathways that are implicated in the pathogenesis of monogenic SLE, including the complement system, type I IFN production, apoptosis, nucleic acid sensing, nucleic acid degradation and self-tolerance. This group has an increased risk of morbidity and mortality, which may be associated with long exposure to disease damage. Comorbidities and increased toxicities may complicate the treatment of lupus in the old age [50]. The causes of death also differ with age. In LSLE patients, infections, cardiovascular diseases and malignancies are the most common causes of death, whereas higher disease activity is the most common cause of death in JSLE patients [51, 52]. This may reflect the decline of the immune system with the aging process and increased comorbidities. Interferon α (IFNα) production which is critical in SLE pathogenesis, decreases with aging [53]. This can contribute to the milder disease phenotype in LSLE. The number of natural killer (NK) cells and cytokine/chemokine secretion decreases with age, as well [54]. The NK cell dysfunction is related to increased infection rates and mortality in older adults and SLE [55]. Furthermore, total B-cell numbers decrease and B cell compartment changes with aging [56, 57]. And, the number of plasmablasts after vaccination decreases [58]. These changes may be a reason for the decreased antibody response after vaccination, and the increased risk of infection in SLE patients.

**Conclusion**

With novel methods for diagnosis and effective treatment strategies, SLE patients can reach older ages. Thus, we learned that the SLE phenotype shows a spectrum from childhood to old age. This may be related to genetic factors, hormonal status, immunesenescence or inflammaging. SLE patients may exert the biological hallmarks of aging earlier due to the disease pathogenesis. Studies on drugs targeting age-associated signaling pathways in SLE patients could enable better interventions, avoid disease-related harm, and restore vitality. This may also maintain and prolong the quality of life of SLE patients as they age.
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