

Systemic Lupus Erythematosus Detected in Males in the Population of Slovakia

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Abstract

The objectives of this paper are to analyse the incidence of the main gender-specific clinical manifestations and initial therapy at diagnosis of systemic lupus erythematosus (SLE) in the Slovak population. An observational study of SLE men patients (n=66) seen at National Institute of Rheumatic Disease between 1992 and 2014 was performed. Demographic and clinical data were retrospectively collected from hospital records and random selection of women patients (n=50) was selected for comparison.

The average age at the time of disease diagnosis in the male population was statistically significantly higher (35 ± 16.9 years) as compared to the average age of women (24.0 ± 9.1 years). A higher risk of developing chronic renal failure in male SLE has been reported in several studies. In our study we did not find differences between men and women in the occurrence of clinical symptoms of renal damage at the time of diagnosis of SLE. The most frequent first symptom of the disease in men was arthritis (46.9%) as compared to women where the most frequent symptom was skin manifestations (47.8%).

Understanding the differences between male and female SLE will contribute to a timely diagnosis and well-targeted therapy.

Keywords: SLE in men; Clinical symptoms; Renal disorder; Therapy

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Introduction

Systemic lupus erythematosus (SLE) is a clinically heterogeneous autoimmune disease characterized by the presence of autoantibodies targeted against nucleus antigens. Etiology of the disease remains unclear, although it has been shown that multiple genetic and environmental factors may play a role in its pathogenesis. Autoimmune diseases (AID) are associated with a marked genetic susceptibility. Female gender seems to be a risk factor for autoimmunity, with a 2.7 times higher risk of autoimmune disease in women than in men [1] and 9:1 female-male ratio in SLE [2]. Autoimmune diseases more frequent in men are characterized by acute inflammation, the range of autoantibodies and typical proinflammatory Th1 immune response, while AID more frequent in women is associated with antibody-mediated pathology. In addition, AID affecting more frequently women that occur around the age of 50 is associated with Th2-mediated immune response. Variability of clinical manifestations of SLE is reflected also in their differences between men and women. The outcomes of individual studies differ due

to low numbers of patients in most of them, variable duration of follow-up and different course of the disease in individual ethnic populations [3,4]. Sex differences may influence the clinical and serological expression, therapy and outcome. The aim of this study was to analyse the incidence of the main gender-specific clinical manifestations at diagnosis of the disease, in the Slovak population and initial therapy at diagnosis.

Materials and Methods

All patients with SLE in Slovakia are at least once in their lifetime examination or hospitalized in the National Institute of Rheumatic Diseases Piešťany (NIRD). In our retrospective study we focused on evaluation of clinical manifestations in 66 men were examined in NIRD and random selection of women patients (n=50) was selected for comparison. Demographic and clinical data were retrospectively collected from hospital records. Clinical manifestations in this study were determined according

to criteria set by the American College of Rheumatology (ACR) [5]. Time of diagnosis was the date at which an individual patient met at last four ACR criteria.

Statistical Analysis

Features from the different domains were compared between the 2 groups (men and women) using descriptive statistical test and Student's t-test for continuous variables.

Results

The analysis was based on the medical records archived in the NIRD, of all male patients hospitalized in the Institute of Rheumatology Piešťany between 1993-2014. The average age at the time of disease diagnosis in the male population was statistically significantly higher (35 ± 16.9 years) as compared to the average age of women (24.0 ± 9.1 years). The age distribution at the onset of SLE in men and women is shown in **Figure 1**. The average time interval between the onset of the first symptoms and establishment of diagnosis was 6.5 months in group of men.

Frequency of individual clinical manifestations at the time of SLE diagnosis is shown in **Table 1**. The most frequent first symptom of the disease in men was arthritis (46.9%) as compared to women where the most frequent symptom was skin manifestations (47.8%). Other frequent manifestations in men included serositis (45.4%) and renal disorder (nephritis) (40.9%). On the contrary, ulcers in the oral cavity, alopecia and fever were observed less often at SLE diagnosis in men. In group of women, in addition, the most frequent clinical manifestations of the disease include skin manifestations, arthritis, renal disorder and hematologic manifestations.

Glucocorticoids are the most commonly used drugs for the treatment of SLE for both genders, such as at the beginning of the disease, and in its course (**Figure 2**). In a group of men except for corticosteroid therapy predominated methotrexate and pulse therapy of cyclophosphamide.

Discussion

Several studies published in recent decades describe gender-specific differences between clinical and laboratory parameters in patients with SLE. The data differ according to the size of the groups compared, ethnicity and duration of the studies. Our study covered a significant period, with the oldest medical record

dating back to 1993. On the other hand, it was impossible to compare laboratory parameters, as the laboratory methods have changed over time.

The average age at the time of disease diagnosis in our group was 35.0 ± 16.9 years in men which is statistically significantly higher than in women (24.0 ± 9.1 years). The age range in the literature is reported at 26-55 years [6-9]. Two studies of the Caucasian population [10,11] document statistically higher age in men than in women, while other studies [2,12,13] do not report statistically significant difference in age at diagnosis, between men and women. We have noticed in men a shorter time interval between the first symptoms of the disease and its diagnosis. In our group the average interval was 6.5 months (range, 3-27 months) in men as compared to 10.5 months in women [14] Molina et al. report the interval of 6-46 months until establishment of the diagnosis in men [15].

We found a high prevalence of use of glucocorticoids in our population men and women at the time of disease diagnosis and high prevalence of use of glucocorticoids persist in Population in the course of the disease as reported [16]. Their research showed that 89% of patients remain long-term treatment with corticosteroids. Two-fold higher prevalence of treatment with i.v. pulse therapy of cyclophosphamide and methotrexate in group of men reflects an increased incidence of arthritis and serositis at the time of diagnosis of SLE diagnosis. Renal disorder (lupus nephritis - LN) is one of the main complications in SLE and the most frequent cause of morbidity and mortality of patients with SLE [17]. In our group, renal symptoms were the second main manifestation of the disease at its diagnosis in men. A high prevalence of renal disorder in patients with SLE is reported

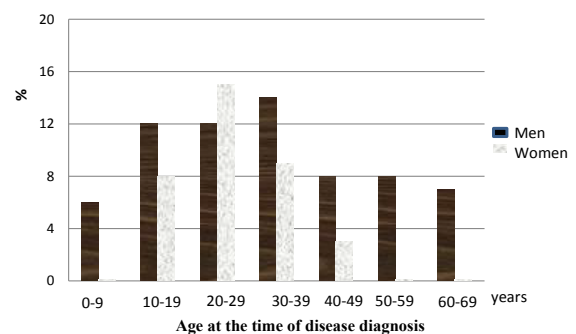


Figure 1 Age distribution of patients at the time of the SLE diagnosis.

Table 1 Clinical symptoms at the time of disease diagnosis.

Clinical manifestation	Men (n=66)	Women (n=50)
Arthritis (n(%))	31 (46,9)*	12 (33,3)
Fever (n(%))	0 (0)*	4 (11,1)
Alopecia (n(%))	0 (0)*	3 (8,3)
Raynaud's sy (n(%))	8 (12,1)	2 (5,6)
Photosensitivity (n(%))	2 (3)	2 (5,6)
Skin manifestations (n(%))	23 (34,8)	14 (47,8)
Hematologic manifestations (n(%))	20 (30,3)	11 (30,5)
Serositis(n(%))	30 (45,4)*	9 (25)
Renal disorders (n(%))	27 (40,9)	13 (36,1)
Neuropsychiatric symptoms (n(%))	7 (10,6)	3 (8,3)

*p value was <0,05 between group men and women

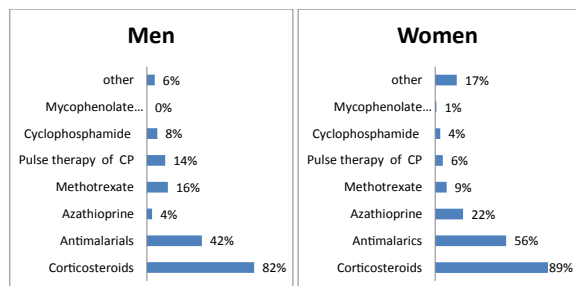


Figure 2 Initial therapy of the diagnosis of SLE.

previously by several authors [15,18] and the most common type is diffuse proliferative glomerulonephritis [19,20]. De Carvalho et al. did not confirm increased LN prevalence [17]. They did not observe differences in histological distribution of nephritis, but they stated that men had a higher LN activity and higher creatinine levels as compared to women. A more frequent symptom in men in our group was arthritis (46.9%), which accounted in women for 33.3%. Font et.al on the contrary, pointed out a lower incidence rate of arthritis and skin exanthema during the follow-up [12]. No differences were observed in this study as for the presence of nephropathy, or general renal dysfunction. At the time of diagnosis, the most common clinical symptoms of the disease in all Slovak SLE patients were blood count pathology, lupus rash, photosensitivity, kidney involvement and positive anti-nuclear antibodies. More than half of patients (52%) presented with lupus nephritis either initially or later during the course of the disease, while in 18% the condition was evaluated as deteriorating or non-stabilized with repeated waning (periods of remissions) and waxing (periods of relapses or flares) [16]. Danish authors [10] noticed increased prevalence of nephropathy and serositis and a lower incidence of photosensitivity in men. The incidence of serositis was relatively high also in our group of men (45.4%).

Erythema and photosensitivity was in our group lower in men than in women, which correlates with several other studies [2,7,18,21]. The most common manifestations of the disease at diagnosis in women included lupus exanthema (47.8%), renal disorder (36.1%) and arthritis (33.3%).

Stefanidou et al. report that male gender may be a worse prognostic factor for the disease [22]. Despite similar characteristics of the disease to those in women, the reason for its worse course in men remains unclear. One possible explanation may be the difference in the sex hormone levels. Sex hormones are probably responsible for susceptibility to AID through modulation of Th1/Th2 response [23]. Estrogens are involved in formation of Th2 cytokine profile SLE and androgens are associated with formation of Th1 cytokine profile such as rheumatoid arthritis. Despite the known relations of estrogens and increased incidence of autoimmune diseases in

women, there are an ever growing number of reports of various manifestations of the disease and difference in SLE severity in men as compared to women. According to a recent study published by Crosslin and Wiginton [24] male patients with SLE are more likely to have cardiovascular and renal comorbidities compared with female patients, who, however, have significantly greater odds of diagnoses of urinary tract infection, hypothyroidism, depression, esophageal reflux, asthma, and fibromyalgia.

Conclusion

The published studies have revealed also differences in immune response, when women have a stronger cellular and humoral immune response as compared to men [24,25]. For instance women older than 6 years have elevated IgM levels [26] the tendency to secrete more IL-4, INF γ , IL-1 and have a greater share of CD4+ T lymphocytes as compared to men [27,28]. Estrogens enhance synthesis of cytokines stimulating B lymphocytes to increase production of antibodies and suppress cellular immunity [29]. They induce autoantibodies in non-autoimmune C57BL/6 mice and impair immune complex glomerulonephritis of MRL/lpr mice [30].

Other mechanisms that may contribute to predominance of women in autoimmune diseases include fetal microchimerism, inactivation of X chromosome and its abnormalities [4]. Similarly, gender-specific differences in gene expression may play an important role in severity and clinical course of autoimmune diseases [28].

Marked gender-specific differences in SLE incidence indicate that sex factors (including genetic and hormonal effects) may play an important role in etiology and pathology of this disease. Understanding the differences between male and female SLE will contribute to a timely diagnosis and well-targeted therapy.

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