Influence of Secondary Antiphospholipid Syndrome and Secondary Sjögren's Syndrome on Patient's Quality of Life with Systemie Lupus Erythematosus

Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown etiology with involvement of many tissues and organs that develops due to the presence of specific antibodies in the serum. The disease is characterized by a variable course and periods of exacerbations and remissions. SLE negatively affects the quality of life and shortens life expectancy of affected patients. SLE is often accompanied by secondary antiphospholipid (APS) and Sjögren's (SS) syndrome. APS involves arterial and venous thrombosis leading to multiorgan failure. SS, which involves exocrine glands, causes inflammation which manifestes itself by an impaired production of tears and saliva with a significant impact on life quality.

Quality of life according the WHO definition involves all aspects of human life. In medical sciences the quality of life depends on the health status. There are many questionnaires available regarding the QOL. Some authors conducted a decrease in QOL in patients with SLE, SS and APL.

Keywords: Systemic lupus erythematosus; Sjögren's syndrome; Antiphospholipid syndrome; Quality of life; NHP; SELENA-SLEDAI index; BILAG index; SLICC

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Introduction

In recent years in the literature more attention is paid on patient's quality of life (QOL) with chronic diseases, including systemie connective tissue diseases. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown etiology with involvement of many tissues and organs (skin, joints, mucous membranes, lungs, heart, kidneys, hematopetic syndrome, CNS, PNS, and haematologic features, limphadenopathy, splenomegaly, liver, GI tract and ophthalmic features) and an expanding course due to the presence of specific autoantibodies in the serum. SLE is characterized by a variable course, with flares and remissions.

The presence of SLE, which seizes many organs and tissues, negatively impacts on the patients' heath and thus of their QOL. SLE is relatively often accompanied by antiphospholipid syndrome (APS) and Sjögren's syndrome (SS). APS evolves to arterial thrombosis, venous thrombosis, thrombosis within the capillaries, as well as damage to the endothelium, and thus damages the vessels of many tissues and organs, resulting in a negative impact on the QOL. SS, in which exocrine glands are targeted, manifested as impaired production of tears and saliva, and therefore significantly interferes with patient's QOL.

Systemic lupus erythematosus

The prevalence of lupus is estimated 15-50 per 100000 populations, more frequently among African Americans and Asians, and the incidence of 3-5 persons per 100000 people [1]. The disease affects 6-10 times more women than men and usually develops in people between 16 and 55 years of age.

The pathogenesis of SLE is not known. An important role in the development of disease attributed to genetic factors [2-7] (including antigens HLA class II DR2, DR3 [8], but many other genes outside of this system) [4,9-14], hormones, [15-17] (estrogen effects [18-21] and prolactin inducing autoimmune response), environmental factors [22] (exposure to ultraviolet radiation [23], retroviral infection, EBV, some drugs: procainamide, penicyllamine, isoniazid, methyldopa, chlorpromazyne, interferon alpha, hydralazine) [24].

In SLE there is a complex of immune disoders, of both cellular response (abnormal suppresion of T cells, the formation of autoreactive T cells T CD4, disorders of secretion of IL-2) and humoral response (production of pathogenic autoantibodies with high specificity b y B cells), as well as the production of immune complexes with their participation of disorders of apoptosis and the removal of circulating immune complexes [25- 27].

A. Autoantibodies found in SLE [28, 29]:

B. Antinuclear antibodies ANA (the prevalence in SLE patients 95-100%) are autoantibodies reactive with the antigens of the cell nucleus, including:

C. Anti ds-DNA (double-stranded DNA) antibodies - the prevalence in SLE patients 40-90%), their titres correlates with disease activity, and is associated with renal involvement.

D. Anti Sm (Smith) antibodies - the occurance in SLE patients 5-10%, related to CNS involvement [30,31].

E. Anti SS-A/Ro antibodies - the occurence in SLE patients 30-40% [30,31].

F. Anti SS-B/La antibodies - the occurence in SLE patients 10-20% [30,31].

G. Anti nucleosome antibodies - the occurence in SLE patients 50-70%, related to renal disease [30,31].

H. Anti ribosomal P protein antibodies - the occurence in SLE patients 10-20%, related to renal disease and CNS involvement [30,31].

I. Anti U1 RNP antibodies - the occurence in SLE patients 10%, associated with MCTD [32].

J. Anticardiolipin antibodies [33].

SLE is recognized on the basis of the classification criteria of 2012, with was developed by a group of SLICC (Systemic Lupus Collaborating Clinics) [34]. They are an extension of the criteria from 1997. This includes 11 clinical criteria and 6 immunological criteria. For diagnosis, it is necessary to have at least 4 of the criteria, including at least one clinical criteria and one immunological, or when the patient has a diagnosis of lupus nephritis confirmed by a kidney biopsy and the presence of ANA or anti dsDNA antibodies.

Confirmation of symptoms of SLE and determining its activity has created the need to form tools to assess disease activity and existing organ damage. To assess the activity of SLE we use the following scales: SLEDAI [35], SELENA-SLEDAI [36], and BILAG [37].

SLEDAI (the scale of Systemie Lupus Erythematosus Activity Index) [35] summarize 24 parameters that include various symptoms of this disease. 19 parameters assessing 9 organ systems. Each parameter is assessed as present or absent within 10 days of the examination. The maximum number in SLEDAI is 105. The symptoms of the CNS can score up to 56 points, while the kidney symptoms - 16.

Categories of disease activity

a. Inactive - SLEDAI = 0

b. Mild - SLEDAI = 1-5

c. Moderate - SLEDAI = 6-10

d. High - SLEDAI = 11-19

e. Very high - SLEDAI = 20

With disease progression, a variable of + 8 is annotated, while improvement of disease is annotated - 6. Scale SELENA-SLEDAI (Safety of Estrogen in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index) [36] evaluated in the last 10 days. This is the simplest scale covering essential groups of symptoms of SLE. The scale takes into account the basic and common characteristic clinical symptoms of SLE, hematological and immunological activity, but not all the symptoms of SLE fall into this scale. The scale is used to monitor the effectiveness of treatment and numerical assessment of the degree of its deterioration. The specific listed, are pointed 8, 4, 2 or 1 respectively - depending on the severity changes of lesions. The highest score - 8 points - results from neurological symptoms and vasculitis. Arthritis and renal symptoms are allocated 4 points and the rest more important symptoms depending on the activity of SLE, 2 or 1 point. The maximum number of points on the SELENA-SLEDAI is 105 points.

The rate of exacerbations of the disease SELENA-SLEDAI Flare Index

a. Mild to moderate deterioration, which corresponds to the increase in the SELENA-SLEDAI index 3 points or more (but not more than 12). They relate to the deterioration or the appearance of new symptoms, skin-mucosa, muscles, pleuritis, pericarditis, arthritis, fever and increasing the dose of prednisone, but not > 0,5 mg/kg/day, adding NSAID or hydroxychloroquine (or other anti-malarial drug) to treatment due to deterioration of SLE, increasing on the scale Physician's Global Assessment (PGA) >=1 (33 mm), but not more than 2,5 (83mm);

b. Severe deterioration, i.e., those which corresponds to the increase in the SELENA-SLEDAI index by more than 12 points. They relate to the deterioration or the appearance of new symptoms from CNS, vasculitis, kidney, polymyositis, hemolytic anemia, Hgb < 7 g/dL or reduction Hgb > 3g/dL, thrombocytopenia < 60000, the change in treatment consisting of increasing the dose of prednisone > 0,5 mg/kg/day or administration of IV pulses, and the need to administer other immunosuppressive drugs (cyclophosphamide, azathiopryne, methotrexate, increase in PGA score above 2,5 (83 mm).

The diosease activity according to SELENA-SLEDAI

a. Mild < 6 points

b. Moderate - 7 - 12 points

c. High > 12 points

The scale of the British Isles Lupus Assessment Group - BILAG [37]. BILAG scale assesses the course and evolution of changes in SLE within 4 weeks of the examination and allows comparison of the current clinical picture with the earlier disease state. By examining patients regularly during a period of 3-months and assessing the scale, a more precise assessment of the evolution and changes of the disease activity is done. The scale specifies a whole spectrum of multi-organ symptoms of SLE, dividing them into eight organ-specific groups. The scale assess of 86 individual symptoms related to SLE. Each symptom describes not only its current presence (present / absent), but also whether it is a new symptom or a recurring symptom if the changes have improved or are stable and have not changed since the last evaluation.

The scale BILAG also takes into account the severity of symptoms. They distinguish between symptoms of low degree (mild) and severe symptoms (severe). In some groups of symptoms, such as eg., arthritis, they separated the moderate degree of lesions (moderate), specifying the definition of the different stages of advancement.

BILAG consists of 9 groups of symptoms: general, mucocutaneous, neurological, musculo - skeletal, cardiovascular and pulmonary, gastrointestinal, ophthalmic, renal, hematologic. Criteria score:

0 - No change

1 - Improving

2 - No changes compared to the previous period

3 - Worsening

4 - New symptom

Evaluation of activity of systemic lupus erythematosus scale BILAG

Result A - active, severe illness, when there is 1 new symptom - 4 points, or 2 signs of deterioration - 3 points

Result B - moderately severe disease, when 1 symptom is worsening - 3 points

Result C - disease condition stable, without changes compared to the previous period - 2 points

Result D - improvement, symptom that appeared previously disappeared or is recovering.

The damage indicator SLICC (Systemic Lupus International Collaborating Clinics / American College of Rheumatology) [38] assess 10 organs and the presence of diabetes and cancer. It reveals organ damage in patients with lupus, but does not indicate the cause of the damage that can result from a highly active disease, it may be caused by treatment or arise as a result of a surgical procedure or the presence of cancer. To avoid confusion between acute inflammation and damage, symptoms must be present for at least 6 months. It is estimated that inflammation lasting six months can cause tissue damage. Damage does not include symptoms like hematological cytopenias, because the damage should be able to be documented eg. Magnetic resonance imaging or computed tomography. Individual symptoms of organs are assigned a specific point value - from 1 to 3. The maximum possible score on this scale is 47 points. High rates of permanent damage in the early stages of the disease are a bad prognostic factor and is associated with increased mortality. Therefore SLICC / ACR Damage Index should be assessed at least once a year.

Bruce et al. [39] in a recent study conducted within the group SLICC (System Lupus International Collaborating Clinics) published in the Annals Rheumatic Disease in September 2015 analyzed data from 1,722 patients (mean age 35 years) with the new (disease duration <= 18 months) diagnosed with SLE treated at 31 centers in 11 countries in 2000-2011. Rate SDI was evaluated each year of observation and underwent steady growth. The occurrence of changes in organs increased the risk of another change. Based on statistical analysis, several factors emerged, contributing to the occurrence of both the first lesion, as well as the progression of existing lesions. Contributory factors include: older age, origin (African Americans), the SLEDAI scale, the use of glucocorticoids and hypertension. Male sex and origin (Caucasian Americans) were correlated with the increase in SDI from 0 to> = 1. The use of antimalarial drugs reduced the risk of organ damage. The results can be a valuable clue in the next update of recommendations for the treatment of systemic lupus erythematosus, as some of these factors are subject, of to modification, which will improve the prognosis for patients with SLE.

Sjögren's syndrome

SS is a chronic autoimmune disease characterized by the infiltration of lymphocytes within the exocrine glands, and other organs and systems, resulting in their functional impartment [40].

The incidence of SS is determined to be between 0.1-5% of the population, except that it is more prevalent in women (9:1) and most often develops in those over the age of 40-50 [41]. SLE is often associated with SS [42].

The pathogenesis of SS is not known. An important role in its development are genetic factors (including HLA DR2, HLA-DR3, HLA-B7, HLA DQ) and environmental (viral infections, CMV, EBV, HTLV1, HIV, HCV and UV radiation) [42].

In SS tends to infiltration T lymphocytes, especially CD4, CD8, and as well as B lymphocytes, showing characteristics hyper reactivity within the exocrine gland and around other organs [42].

Hyperactivity of B cells is expressed by the presence of circulating auto antibodies (RF, antibodies to SSA / Ro, SSB / La).

There are two forms of Sjögren's syndrome: primary and secondary, which accompanies other autoimmune diseases.

Patients complain of a feeling of sand under the eyelids, a burning sensation, redness, itching eyes and photophobia due to the infiltration of lymphocytes in the tear gland, resulting in dryness of the cornea and conjuctiva. The involvement of other exocrine glands occurs less frequently, and can occur as abnormal secretion of mucous glands of the upper and lower respiratory tract and can cause dryness in the oral, nasal, throat and bronchi. Infiltrated glands in the gastrointestinal tract can lead to inflammation of the esophagus, atrophic gastritis, and pancreatitis. Infiltrated glands in the genital organs can cause vaginal dryness, and consequently painful intercourse. Infiltrated glands in the skin results in dryness and itching.

Changes in the motor system are common and include pain and/or inflammation of the joints, without erosive arthritis. Changes in the pulmonary system leads to dryness and a higher incidence of infections, persistent dry cough, and interstitial pneumonia, nodular lesions in the lungs or changes related to the development of lymphoma and rarely lymphocytic alveolitis [43]. Changes in the kidneys can lead to the development of tubular acidosis, or glomerulonephritis. Vasculitis in SS can cause purpura, recurrent urticaria and ulcers of the skin [44]. Changes in the nervous system resulting from vasculitis, may involve both the central and peripheral nervous systems. The most common syndromes is peripheral neuropathy, however transverse myelitis, paralysis and seizures may also occur [45].

SS classification criteria are developed by the American College of Rheumatology (ACR) from 2012 [46].

I. Positive anti-Ro and/ or anti-La antibodies or a positive ANA level of 1 : 320 or greater, or a positive rheumatoid factor (RF)

II. A positive labial gland biopsy defined as at least one periductal focus of 50 or more lymphocytes per 4 mm2 high powered fiels.

III. A newly devised ocular staining score (OSS) of 3 or greater.

Diagnosis is possible when 2 of the 3 criteria are met. The activity of SS is examined on ESSDAI scale [47]. ESSDAI scale was developed for the assessment of disease activity in patients with primary SS. 12 domains of symptoms include constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, PNS, CNS, Haematological, biological. Each domain is divided into 3-4 levels of activity, which are defined by a detailed description. Moderate disease activity is defined as ESSDAI ≥ 5. The minimum in clinically significant remission of disease activity is a reduction of at least 3 points.

Antiphospholipid Syndrome

APS is an autoimmune disease, caused by antiphospholipid antibodies forming thrombi, which may affect venous, arterial, capillary or obstetric complications.

APS may be primary or secondary (accompanying other autoimmune diseases, especially SLE and proliferative infections). The prevalence of APS is estimated to be 40-50 per 100 000 population, the incidence of 5 per 100 000 population, more women are affected (3.5:1).

The pathogenesis of APS is not known. Genetic factors and infections may contribute to its development [48,49]. APS is diagnosed on the basis of the modified Sapporo classification criteria [50].

Clinical Criteria

Vascular thrombosis

One or more clinical episodes of arterial, venous, or small-vessel thrombosis, with the exception of superficial venous thrombosis, in any tissue or organ. Thrommbosis nmust be confirmed using imaging or Doppler studies or histopathology. For histopathological confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

Pregnancy morbidity

One or more unexplained death of a morphologically normal fetus at or beyong the 10th week of gestation

One or more premature birth (<34 weeks of gestation) of a morphologically normal neonate, because of eclampsia, severe pre-eclampsia and placental insufficiency.

Three or more unexplained consecutive spontaneous abortion before the 10^{th} week of gestation (excluded maternal anatomical or hormonal abnormalities and chromosomal cause.

Laboratory Criteria

Lupus anticoagulant is considered positive if present in plasma, on two or more occasions at least 12 weeks apart. Anticardiolipin antibodies of IgG and/or IgM isotype bif present in serum or plasma, in medium or high titre, on two or more occasions, at least 12 weeks apart. Anti-beta2-glycoprotein I antibodies of IgG and/or IgM isotype, if present in serum or plasma, on two or more occasions, at leat 12 weeks apart. Diagnosis is possible when 1 clinical and 1 laboratory criteria are met.

Quality Of Life

According to the WHO definition [51], quality of life (QOL) is a subjective assessment by his or her life situation in relation to the culture in which the individual lives, its system of values, objectives, expectations, interests.

Methods for evaluating the QOL are different. QOL can be assessed using a spontaneous utterance of a subject following general the question of "how Mr./Ms feels?" or formulated through a series of questions, psychometric tests and standardized questionnaires. The results obtained using standardized questionnaires, enable most fully their comparison between different studies. Questionnaires are distinguished between general and specific, which relate to a particular disease or group of diseases. Questionnaires describe QOL, which focus on those aspects that are particularly important in the population for which they were designed.

The questionnaires are used for different types of questions: closed (yes or no), point analog scale (answers are ranked from lowest to highest severity), visual analog scales (in the form of a segment of a certain length and mark the start and end points).

Nottingham Health Profile (NHP) scale assesses physical, social and emotional states. It is divided into two parts: the first contains 38 questions and answers: yes or no. The scale examines physical mobility, pain, emotional reactions, energy levels, sleep, and social isolation. The second part consists of 7 questions about homework, employment, social and sexual relationships and personal interests. It uses parameterized evaluation to determine the severity of the particular changes. The questionnaire takes 10 minutes [52].

The Medical Outcomes Study 36-item Short Form (SF-36) assesses the general health of SLE patients. It comprises eight multi-point scale consisting of 2 to 10.The scale relates to physical health, mental health, social functioning, role occupied in society, general health and vitality. SF-36 which covers 8 scales summarizes the patient's physical and mental health. The scale consists of questions about the health over the last week or month. The questionnaire takes 10 minutes [53,54].

The loss of function study is most commonly used Health Assessment Questionnaire (HAQ) [55], asking about the physical and mental disability, pain, general discomfort, employment, income, cost of medical care and side effects of treatment. Assessment of physical capacity is determined on the basis of a questionnaire filled out by patients. Questions raised in this questionnaire reflect everyday and basic activity of the patient. HAQ is very sensitive to clinical changes. It consists of 8 groups of basic questions and 24 specific, relating to: 1. Dress and personal care products, 2. Get up from bed, 3. Food, 4. walking 5. Hygiene, 6. Stretching, 7. Grasping 8. Motor function. Additional questions concern ancillary improvements, or equipment used in carrying out these activities.

The patient has to choose one of four possible answers to the question (0 - no difficulty, 1 - with some difficulty, 2 - with great difficulty, 3 - impossible to do). The overall result is obtained by summing up the points for each reply (from 0 to 3 for each answer). The test takes 10 minutes. It was created as a modified Health Assessment Questionnaire (M - HAQ) [56]. HAQ and MHAQ

are standard questions talking about disability.

In comparative studies HAQ was compared with traditional methods of measuring the number of tender and swollen joints, a 10-cm visual analog scale VAS for pain and patient global assessment on arthritis.

Quantitative assessment (so-called VASP (Visual Analog Pain Scale) - visual pain scale) is to determine the patient's visual analogue pain scale (it is a 100 mm line) to rate their currently occurring pain. You should instruct the patient that the starting point from the left side corresponds to no pain, and the end point on the right side is maximum, unbearable pain.

The Study Of QOL In SLE Patients

The study of QOL in SLE patients was performed and documented by many authors.

Schmeding and Schneider [57] reviewed the literature from 2000-2010 on the QOL of patients with SLE. It has been shown to lower QOL in patients with SLE vs. patients with other chronic diseases. SLE significantly reduces patients' ability to cope with everyday activities. It is conditioned by age, fatigue and coexistence of neurological and psychiatric disorders, depression and irritability. There was no direct correlation between the degree of disease activity and organ damage in SLE and QOL.

Choi et al. [58] evaluated that the QOL of patients with SLE was lower than the control group, consisting healthy people. Reduced QOL resulted in depression, taking GCS and fatigue, which was not the result of the degree of disease activity and organ damage. Understanding psychological problems and appropriate treatment can help to improve the QOL of patients with SLE, especially those taking high doses of glucocorticosteroids, even if the disease activity is low. The study included 108 patients with SLE, the control group were 52 healthy people.

Almehed et al. [59] found that the QOL in patients with SLE is lower than in the general population, and the ability to work means better health of patients with SLE. The study involved 163 women with SLE, the control group consisted of 1,045 people. Similarly Zuily et al. [60] found that in the general population, patients with SLE have a lower QOL. In these patients, congested blood was a common finding,, which compromise their QOL.

Balitsky et al. [61] found that the coexistence of SLE and thromboembolic complications have a much greater negative impact on the QOL of patients without associated thromboembolic complications of SLE or APS. The study included 882 patients. Used form SF 36.

Georgopoulou et al. [62] showed that patients with primary APS have fewer physical symptoms than patients with SLE and secondary APS, resulting in a better QOL. In the group of patients with primary APS symptoms related to mental state occurs more frequently, so it is important to provide them with adequate social support and deliver the right amount of information about their disease and the current stage of the disease. The study included 270 patients used a scale SF 36.

Zuily et al. [60] evaluated the QOL in patients with APS. Researchers have shown that the QOL of patients with APS is lower than in healthy volunteers. In this group, thromboembolic complications are more frequent. The study included 115 patients, including 53 with APS. QOL tested using the SF 36.

In a prospective study [63] authors were interested in the presence of headaches in patients with lupus. Headaches are common in SLE, but are not associated with disease activity or the level of specific antibodies. Although headaches are associated with a lower QOL, their intensity decreases with time and treatment used.

Yilmaz-Oner et al. [64] showed that patients with SLE suffer more often from mood disorders, depression, anxiety than in healthy population. The authors suggest that clinicians should pay attention to the symptoms of mood disorders and depression in patients with SLE and effectively treat them to improve the QOL. The study enrolled 113 patients with SLE and compared them with a group of 123 healthy people. The study used questionnaires SLEDAI, HAPS and SF 36.

Pettersson et al. [65] found that fatigue in patients with SLE is more common, is associated with depression, annoyance and lack of physical activity. Patients with SLE who lead active lifestyles experience less fatigue, compared with people with SLE showing no physical activity. The study involved 305 patients with SLE and 311 people in the control group. Fatigue Severity Scale (FSS), Vitality (VF SF-36) and Multidimensional Assessment of Fatigue scale (MAF) was used. Further features of the problems were social alienation (median 22.0 statistically significantly greater severity than the control group, $p = 0.0014$) and limited movement (median 22.0, but no statistical significance in relation to the level of the control group). The least number of patients were troubled by sleep disorders (median 0 in both groups), and physical pain, they were located on exactly the same level as the control group.

Mirbagher et al. [66] found that the poor quality of sleep is a common symptom in women with SLE, which significantly affects their QOL. It is determined by age, disease activity and psychological factors. The study included 77 women with SLE and the Pittsburgh Sleep Quality Index (PSQI) was used.

Priori et al. [67] assessed the quality of sexual life. They found that the quality of sexual life in women with primary SS, both during pre- and postmenopausal women have a lower quality of sexual life caused by dyspaurenią. The study included 24 women, and the Female Sexual Function Index (FSFI), Hospital Anxiety and Depression Scale (HSDS) and SF 36, was used. In lupus QOL is impaired especially if it coexists with a secondary diseases.

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