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Systemic lupus erythematosus in the elderly

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, characterized by multisystemic involvement. Late onset SLE represents a specific sub-group of the disorder, beginning above 50–65 years of age. The incidence of late onset SLE ranges in the interval of 12–18% and the course of the disease is considered to be more benign. According to several authors, skin manifestations, photosensitivity, arthritis and nephritis, occur rarely in the elderly patients with late SLE onset; prevalence of serositis, lung involvement and Sjögren's syndrome were observed more often. Late onset SLE patients manifested higher rate of positive findings of rheumatoid factors, as well as of anti-Ro and anti-La antibodies; and the lower occurence of anti-RNP antibodies and hypocomplementaemia. A slow onset of the disorder, non-specific manifestations at the beginning of the illness and less frequent prevalence of SLE in the elderly often result in late diagnosis. Treatment of the disease depends on its clinical manifestations. NSAID's, antimalarials or low doses of glucocorticoids are used for the less severe forms. Immunosuppressives and higher doses of glucocorticoids are the treatments of choice for more severe organ involvements and complications. A multidisciplinary approach is recommended for the treatment of late onset SLE patients.

Keywords: SLE; Late onset; Clinical picture

Contents

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, characterised by multisystemic involvement, with a broad spectrum of clinical and laboratory manifestations.

Etiopathogenetic factors, which can influence the development of SLE, include, most of all, genetic background of the patient, external environmental agents (eg superantigens, viruses, UV radiation, drugs, chemicals), hormonal milieu, age, and probably also other factors that are as yet unknown. The result is disturbance of the immunologic homeostasis, with resultant induction and production of autoantibodies contributing to tissue damage. [1].

In the course of aging, the immune system undergoes continual morphological and functional changes. In general, as aging proceeds, the ability of the immune

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system to defend the organism against foreign pathogens decreases, while the response to autoantigens increases. In healthy elderly populations, the occurrence of antinuclear antibodies and rheumatoid factors increases [2]. In the course of aging, the number of naive CD45RA T-lymphocytes decreases and the share of memory CD45RO T-lymphocytes increases; the ratio between CD4+ and CD8+ T-lymphocytes expressing CD28 receptor changes, the ability of peripheral blood lymphocytes to proliferate after mitogen stimulation decreases [3,4]. As aging proceeds, the level of serum cytokines and acute phase reactants increases 2–4 times. Inflammatory mediators possibly represent the bridging interconnections between environmental factors, infections and physiological changes in the process of aging; however, they also constitute risk factors for the diseases conditioned by ageing [5]. These changes can contribute to an atypical course of the disease or the occurrence of certain other inflammatory diseases in the elderlyeg polymyalgia rheumatica.

The group of patients who suffer from SLE most frequently is women in their 2nd to 4th decade. [6,7]. Late onset SLE represents a specific sub-group of the disease, which begins above 50–65 years of age [8–10]. The incidence of late onset SLE is rarer, affecting 12–18% of population [6,7,10,11]. The prevalence of women is preserved, even though the ratio of women to men decreases (1,1:1–7:1) compared to SLE beginning in younger age (5,7:1–9:1) [3,8,9,12]. Late onset SLE is more frequent in Caucasian populations. [11,13].

There is an assumption that late onset SLE may have a different clinical course, with an insidious start, the very first manifestations being non–specific. Iinitial clinical manifestations include arthralgias, weakness, fatigue, myalgias, weight loss, pyrexia or loss of cognitive function. [7,14,15]. The clinical course of late onset SLE is considered to be more benign. In the group of late onset SLE patients, skin manifestations, photosensitivity, arthritis and nephritis were less frequent in comparison with the SLE patients in whom the disease began at a younger age [7,11,14,16](Table 1). In late onset SLE, a higher occurrence of serositis, lung involvement and Sjögren's syndrome were observed [7,11,14,16,17]. Lower prevalence of nephritis, CNS involvement and dermal manifestations in the patients in whom SLE began after their 50th year of age was described, among others, by Formiga [8], who assessed their activity score as well. At the beginning and during the first year of their disease, SLEDAI score was lower compared to patients with SLE beginning in younger age. A more benign course of the disease was more often observed in late onset SLE 11 patients (75%) in comparison to younger patients (27%). A lower occurrence of nephritis and more frequent neurological complications in late onset SLE patients was observed by Bertoli [13]. In a somewhat controversial paper by Mak [18], in a predominantly Chinese population, similar prevalence of organ complications (lung, heart, kidney and CNS involvement) were observed in both groups of SLE patients, while the late onset SLE patients showed lower incidence of skin complications and higher incidence of serositis. Madisson [19] observed a higher prevalence of cardiovascular, eye and musculoskeletal complications as well as malignancies in a group of 86 patients with SLE in whom the disease started above 54 years of age.

Table 1
Clinical manifestation of late onset SLE

Authors	Occurrence	
	Reduced	Elevated
Maddison [7]	Polyarthritis	Pulmonary affection
	Alopecia	Sjögren's syndrome
	Raynaud's phenomenon	Anti-Ro, anti-La
	Lymphadenopathy	Rheumatoid factor
	Anti-nRNP	
Baker [11]	Lymphadenopathy	Pleuritis
	Neuropsychiatric manifestations	
	Raynaud's phenomenon	
Cattogio [14]	Arthritis	Pulmonary affection
	Raynaud's phenomenon	Conjunctivitis sicca
	Alopecia	Anti-Ro, anti-La
	Serositis	Rheumatoid factor
	Anti-nRNP	
Wilson [16]	Nephritis	Pleuritis
	Rash	Pericarditis
	Hypocomplementaemia	Arthritis
	Anti-dsDNA	Rheumatoid factor
Cervera [21]	Lupus exanthem	Sjögren's syndrome
	Photosensitivity	
	Thrombosis	
	Arthritis	
	Nephropathy	
	Anti-La	
Ward [22]	Alopecia	Serositis
	Raynaud's phenomenon	Intersticial lung diseases
	Fewer	Sjögren's syndrome
	Neuropsychiatric manifestations	Anti-La
	Hypocomplementaemia	
Boddaert [23]	Photosensitivity	Serositis
	Alopecia	Lung involovement
	Skin vasculitis	Rheumatoid factor
	Neuropsychiatric manifestatons	
	Lymphadenopathy	
	Nephritis	
	Anti-RNP, anti-Sm	
	Hypocomplementaemia	

Kidney, skin and CNS affections were similar in both groups. Organ complications were evaluated according to SDI score, which evaluates 12 organ systems, but it does not take into consideration the reasons of the complications, so they may represent the manifestation of comorbidity, applied treatment and/or the clinical manifestations of SLE.

Late onset SLE may differ also in the frequency and type of autoantibodies. In patients with late onset SLE, a higher prevalence of rheumatoid factors was observed, as well as of anti-Ro, and anti-La antibodies, and the lower occurence of anti-RNP antibodies and hypocomplementaemia [7,12,14,20]. The occurrence of anti-dsDNA antibodies is lower in late onset SLE patients [16,17] or may be similar to younger patients according to some studies. [10,15]. A higher occurence of anti-dsDNA antibodies in late onset SLE patients was observed by Padovan [12], but these antibodies did not correlate with organ complications of the disease.

The differences between individual papers can be explained by rather small sizes of patient groups, varying definitions of age for late onset SLE start (50–65 years) as well as varying time of diagnosis, ethnic differences in the groups of patients, retrospective collating of data and by different methodology of autoantibodies' estimation.

Cervera [21] prospectively followed a group of 1000 SLE patients. In 90 patients (9%) the disease began after their 50th year of age. At the beginning of the disease, these patients had lower occurrence of arthritis, lupus exanthema and nephropathy. In the course of their disease, the prevalence of arthritis, lupus exanthema, photosensitivity, nephropathy, and anti-La antibodies decreased and the incidence of Sjögren's syndrom increased.

The outcome of a meta-analysis published by Ward [22] was the finding of a higher incidence of interstitial lung diseases, serositis, Sjögren's syndrome as well as positive findings of anti-La antibodies in late onset SLE. In these patients, neuropsychiatric disorders Raynaud phenomenon, alopecia, pyrexia, lymphadenopathy and hypocomplementaemia occurred less frequently. No differences were observed in the occurence of nephritis, photosensitivity, myalgias, leucopenia, rheumatoid factors and anti-dsDNA antibodies.

Boddaert [23] analysed data collected from literature via comparing the incidence of clinical manifestations and autoantibodies in the group of 714 late onset SLE patients and 4700 SLE patients in whom the disease began at a younger age. In the elderly patients, higher occurrence of serositis, lung involvement and positive findings of rheumatoid factors was observed as well as lower occurrence of malar rash, photosensitivity, skin vasculitis, alopecia, Raynaud's phenomenon, neuropsychiatric manifestations, lymphadenopathy, nephrotic syndrome and nephritis; as for laboratory parameters, there was a lower occurrence of positive anti-RNP, anti-Sm antibodies and hypocomplementaemia.

SLE diagnosis in all age groups is based on the presence of clinical and laboratory findings according to diagnostic criteria [24]. Because of the slow onset and often, non-specific manifestations at the beginning of the disease, and due tothe less frequent prevalence of SLE in elderly populations, late diagnostis of the disease is quite common. The interval from the first manifestations to the establishment of SLE diagnosis is longer (19–50 months) in comparison with younger patients (5–24 months). [3,8,7,12,14]. The most frequent misdiagnoses include polymyalgia rheumatica, rheumatoid arthritis, osteoarthritis, infections and malignancies; less frequent are primary Raynaud phenomenon, discoid lupus erythematosus, chronic active hepatitis, fibrosing alveolitis, but also tuberculosis, infectious endocarditis, idiopathic thrombocytopenic purpura, chronic renal failure and photodermatitis [7,11,14]. Due to the fact that late onset SLE affects patients with usually higher comorbidity factors, requiring pharmaceutical therapy, the differential diagnosis should also include drug-induced lupus. The clinical picture of this nosological entity also includes muscle and joint disorders, as well as lung involvement, pyrexia and weight loss; in the laboratory picture, antinuclear antibodies are present but anti-dsDNA antibodies and hypocomplementaemia are absent. Drugs that may induce SLE and do so most frequently, include procainamide, isoniazid, methyldopa, carbamazepine, acebutolol, hydralazine, chlorpromazine, sulfasalazine, D-penicillamine and others. [25]. Despite the discrepant findings of the prevalence of organ complications in late onset SLE, the cause of death in the elderly SLE patients is not usually caused by SLE itself, but rather by the more frequent occurence of infections, cardiovascular disorders, malignancies or drug-induced complications. [9,10,13].

Because the reason for SLE development is, as yet, unknown, treatment of the disease is aimed at the suppression of symptomes and autoimmune inflammatory response. The treatment depends on the severity of basic disease. Comorbidities and concomitant therapies often restrict the options for late onset SLE therapy. Possible drug interactions shoulod always be considered and drug-induced disorders as well as changes of pharmacokinetics and pharmacodynamics in the elderly (increasing the risk of side effects) are also important.

The first treatment choice for joint manifestations and serositis are usually NSAIDs or, for a short time, low

doses of glucocorticoids. NSAID treatment begins with low doses, and continues through their slow titration until the efficient dose is achieved, while toxicity and adverse effects of the administered preparations are monitored.

When skin changes and arthritis are manifested, antimalarials are the drugs of choice (chloroquine and hydroxychloroquine), as they have less side effects compared to other drugs used in the treatment of SLE. In patients treated with antimalarials, blood counts, ocular background and possible changes in cognitive functions should all be regularly checked. Lupus pneumonitis and hematological abnormalities require treatment with higher doses of glucocorticoids and, possibly, immunosuppressives. Oral treatment with glucocorticoids is preferred, but in case of more severe complications, intravenous therapy may be required. Lupus nephritis is treated with glucocorticoids and cyclophosphamide, similarly as it is used with younger patients. Regular checking of blood count, liver enzymes and urine sediment are necessary. If cyclophosphamide is contraindicated, azathioprine should be introduced. Neuropsychiatric complications in the elderly are treated symptomatically, and if they represent manifestations of SLE, immunosuppressives are added to therapy. Hypertension and the presence of antiphospholipid antibodies can lead to development of strokes. For prevention of this complication, adequate treatment of hypertension and the administration of acetylsalicyl acid in anti-aggregation doses is necessary, or administration of indirect anticoagulants [2,3,10].

Adverse effects of glucocorticoids include hypertension, imbalance of (eg hypokalemia), hyperglycaemia, hyperlipidemia, CNS changes, as well as a tendency to fluid retention. In long-term therapy, osteoporosis with an increased risk of pathological fractures, avascular necrosis, cataracts and an increased tendency to contract infections have been observed. In the effort to eliminate the risk of the adverse effects development, it is recommended to start the gradual reduction of glucocorticoid dose up to the lowest effective level as soon as the remission is accomplished. Patients are advised to take oral calcium supplementation, vitamin D (also for its immunosuppressive modulatatory functions in doses of 400 IU daily), and gastroprotective preparations.

An important element in the treatment of SLE patients is their proper education about way of life, rehabilitation, avoiding physical strain, direct sun rays and the need to see their physicians regularly.

A multidisciplinary approach is recommended for late onset systemic lupus erythematosus patients. It requires the close cooperation of a rheumatologists, internal medicine specialists, possibly also gerontologists, hematologists, pulmonologists, nephrologists, and, in the case of neurological complications, neurologists and/or, if applicable, other specialists, according to clinical manifestation of the disease. For additional readings which highlight this concept of the Mosaic, we refer to the following papers [26–40].

Take-home messages

- Incidence of late onset SLE is 12–18%
- Clinical course is considered to be more benign
- More frequently Sjögren's syndrome, serositis and pulmonary manifestations.
- Higher occurence of rheumatoid factor, anti-Ro, anti-La antibodies

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Superantigen-induced CD4+ T cell tolerance is associated with DNA methylation and histone hypo-acetylation at cytokine gene loci

Anergy is an important mechanism of peripheral tolerance in which T cells lose the capacity to produce pro-inflammatory cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFNgamma). To determine whether the induction of T-cell anergy in vivo is associated with epigenetic changes that oppose cytokine gene expression, Thomas RM. et al. (Genes Immun 2007; 8: 613-8) measured DNA methylation and histone acetylation at the IL-2 and IFNgamma loci in CD4+ T cells from mice tolerant to a viral superantigen. Tolerant T cells exhibited more DNA methylation and less histone acetylation at the regulatory regions of the IL-2 and IFNgamma genes than effector T cells, which are able to produce IL-2 and IFNgamma. These data show that T-cell anergy in this model is associated with epigenetic modifications that oppose gene expression, and suggest that these mechanisms may be important in the maintenance of tolerance.