The importance of early diagnosis of systemic sclerosis

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Abstract

Systemic sclerosis (SSc) is a connective tissue disease which etiology and pathogenesis is still unknown. The vascular and immunological changes are the major elements of the SSc. The preliminary ACR criteria of SSc are the oldest criteria for rheumatic diseases and are not sensitive enough in respect to early SSc. Many authors suggest that these criteria should be extended by capillaroscopic and immunological changes. In 2001 LeRoy and Medsger proposed new criteria for SSc that could help to identify SSc patients with early stage of the disease. This will give the opportunity for the early and proper treatment.

Key words: systemic sclerosis, early diagnosis.

Systemic sclerosis (SSc) (scleroderma-hardening or sclerosis of the skin) is a connective tissue disease characterized by fibrosis and degenerative changes in the skin and the internal organs – heart, lungs, kidneys and gastrointestinal tract. The etiology and pathogenesis of SSc are unknown but immunologic abnormalities, fibroblast activation, chronic inflammation and vascular damage are considered to be the main elements of the disease [1,2].

Systemic sclerosis is divided into two major variants of sclerodema: Diffuse Systemic Sclerosis (dSSc) and Limited Systemic Sclerosis (lSSc) dependending on degree and extent of cutaneous involvement. LSSc was known as CREST syndrome, where calcinosis, Raynaud's phenomenon, esophageal hypomotility, sclerodactyly and teleangiectasia is observed [2]. These two variants of SSc differ not only in respect to the extent of skin thickening but also in the clinical course and spectrum of internal organ involvement.

In the majority of cases of lSSc the Raynaud's phenomenon is the first manifestation and may proceed skin hardening and the organs involvement for months or years. The Raynaud's phenomenon (RP) is definited as bilateral, episodic di- or triphase (pallor, cyanosis, suffusion) vascular reaction of the fingers, toes, ears or nose [3,4]. This reaction is caused by artery vasospasm. In dSSc the skin and the organs involvement are observed already in first years of the disease. In 90% of SSc patients the immunological changes (the anticentromere and antitopoisomerase-I autoantibodies) are detected. The most patients with SSc have abnormal widefield naifold capillaroscopy with the dilatation and/or avascular areas [3,5].

The American College of Rheumatology (ACR) Preliminary Clinical Criteria for Systemic Sclerosis from 1980 are the oldest criteria of rheumatic disorders [6]. In this preliminary criteria the proximal scleroderma is the single major criteria. Sclerodactyly, digital pitting scars of finger tips or loss of substance of the finger pad, and basilar pulmonary fibrosis contribute further as minor criteria in cases when proximal scleroderma is absent [5]. There are no vascular or immunological changes included in these criteria.

Now after 20 years we know that the absence of cutaneous involvement does not exclude the diagnosis of SSc, which is a mulitisystem, multistage disorder marked by variable manifestation. Difficulty in the diagnosis of the SSc may occur at the early stage prior to development of obvious skin sclerosis. Now it is known that definitive diagnosis may be delayed for several years from the onset of Raynaud's phenomenon until definite characteristic skin changes are seen [5].

During those years significant advances have occurred that have increased our understanding of the pathogenesis of the SSc. In particular it became obvious that immunological and capillaroscopic changes appear already in the earliest phase

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of the disease. The precise autoimmune serology and capillaroscopic evaluation of patients with RP have identified many persons with features of SSc who do not fulfill the preliminary ACR criteria. ACR criteria permit the diagnose of SSc in advanced stages of the disease. Since that many clinicious have suggested that the ACR classification criteria for SSc should be revised to more adequately incorporate those patients without skin sclerosis but with RP, nailfolds capillaroscopy pattern and immunological changes [3,5,7]. Those patients are mainly these with lSSc. Accordingly, Medsger and others, have observed that the ACR preliminary criteria paradoxically exclude patients who have been diagnosed by experienced clinicians as having definite SSc [3]. Therefore in 2001 LeRoy and Medsger proposed the criteria for the classification of early systemic sclerosis [3]. They suggest that typical immunology changes for SSc are: the presence of the selective autoantibodies – anticentromere, antitopoisomerase I, antifibrillarin, anti-PM-Scl, antifibrillin or anti-RNA polymerase I or III in a titer of 1:1 000 or higher. Those autoantibodies should by detected by indirect immunofluorescence using HEp-2 cells as a substrate [3]. Typical capillaroscopic changes include the presence of megacapillaries, avascular areas and/or bushy capillaries.

According to LeRoy et al. for the SSc new classification the RP should be well documented for example by cold stimulation (direct observation of any 2 of pallor, cyanosis, or suffusion, objective evidence of delayed recovery after cold challenge) or by others quantitative measure like laser Doppler ultrasound, termography and others [3,8]. When the RP is documented objectively LeRoy and Medsger proposed RP as the single major criterion for the diagnosis of the most limited cutaneous SSc (lSSc). When the RP is subjective only it is suggested to include both the SSc-typical naifold capillary pattern (dilatation and/or avascular areas) and selective autoantibodies. In LeRoy early classification of SSc the lSSc (limited systemic sclerosis) was proposed when RP plus abnormal nailfold capillaroscopy or SSc selective autoantibodies are detected. LcSSc (limited cutaneous systemic sclerosis) was proposed for CREST syndrome and those patients must have fulfill criteria for lSSc and demonstrate cutaneous involvement distal to the elbows, knees and clavicles. Patients with dcSSc (diffuse cutaneous systemic sclerosis) should match criteria for lSSc and demonstrate proximal cutaneous changes (skin tautness of the arms, chest, abdomen or back) [3] (see *Tab. 1*).

We must also remember about other conditions when RP is observed. The dermatomyosistis and polyarteritis nodosa can be associated with scleroderma-like nailfold capillary abnormalities and RP but their clinical outcome distinguish them from SSc [3,4]. The RP is observed also in diabetes mellitus, hyperviscosity syndromes, hypertension and B-blocker therapy. When the RP is observed the vasculitis, systemic lupus erythematosus (SLE), Sjögren syndrome or an overlape syndrome must be excluded [3,8].

In conclusions many writers suggest that ACR preliminary criteria must have been by microvascular and autoimmune techniques completed [3,5,7]. LeRoy and Medsger considered that by adding nailfold capillary findings and anticentromere serology the sensitivity of ARA classification was improved from 33% to 92% [3].

Table 1. **Constellations of criteria for diagnosis SSc – according to LeRoy and Medsger [3]**

lSSc	lcSSc	dcSSc
RP (objective documented) **plus any one**: SSc-type nailfold capillary pattern **or** SSc selective autoantibodies **or** **RP** (subjective only) **plus both**: SSc-type nailfold capillary pattern and SSc selective autoantibodies	Criteria for lSSc **plus** distal cutaneous changes	Criteria for lSSc **plus** proximal cutaneous changes

lSSc – limited Systemic Sclerosis,
dSSc – diffuse Systemic Sclerosis,
RP – Raynaud Phenomenon

This new proposition for SSc criteria could help to create more sensitive criteria and to minimize false positive diagnoses. The new definition of early lSSc can identify those patients who should be carefully observed for internal organs involvement. Early diagnosis of internal organs involvement will give the opportunity for the early and proper treatment. On the other hand early diagnosis of SSc will allow the studies on the events involved in the pathogenesis of the disease.

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