Available online at www.sciencedirect.com
ScienceDirect
Joint Bone Spine 73 (2006) 490–494
JOINT BONE SPINE
http://france.elsevier.com/direct/BONSOI/

Review

Prognostic markers for systemic sclerosis

Olivier Meyer

Assistance publique–Hôpitaux de Paris, hôpital Bichat, 46, rue Henri-Huchard, 75018 Paris, France

Received 20 October 2005; accepted 30 January 2006
Available online 02 June 2006

Abstract

The prognosis of systemic sclerosis depends chiefly on the extent of the skin lesions, which correlates with the severity of the cardiovascular, pulmonary, and renal manifestations. An erythrocyte sedimentation rate greater than 15–25 mm/h or a hemoglobin level lower than 12.5–11 g/dl is associated with a 2.5- to 3-fold increase in mortality. Anticentromere antibodies are associated with delayed pulmonary hypertension, anti-topoisomerase I antibodies (Scl 70) with interstitial lung disease, and anti-RNA polymerase III antibodies with renovascular hypertension. The risk of death is directly related to the autoantibody pattern. For instance, in a study of 1432 cases from the Pittsburgh Scleroderma Databank, 10-year survival among patients with limited cutaneous disease was 88% in the group with anti-U1-RNP, 75% in the group with anticentromere antibodies, 72% in the group with anti-PmScl, and 65% in the group with anti-Th/To. Ten-year survival in patients with diffuse cutaneous disease was 64% with anti-topoisomerase antibodies, 61% with anti-U3-RNP, and 75% with anti-RNA polymerase III. Several prognostic markers are also available for predicting the risk of organ involvement. For instance, serum levels of KL-6, surfactant proteins SP-A and SP-D, the collagen peptide PIIINP, and homocysteine are associated with the risk of fibrosing alveolitis. Serum levels of CD40L and NP-ProBNP, circulating endothelial cells, and serum anticardiolipin titers correlate with the risk of arterial hypertension. Serum VCAM1 and markers for oxidative stress such as carboxyl terminus residues predict the risk of vascular disease. Other serum markers for organ involvement are under study, although their predictive performance remains to be evaluated.
© 2006 Elsevier SAS. All rights reserved.

Keywords: Systemic sclerosis; Prognosis; Autoantibodies

1. Introduction

Systemic sclerosis (SSc) is a rare disease that is classified by healthcare authorities among the orphan diseases. In a study conducted in the Seine-Saint-Denis region of France, the prevalence of SSc was estimated at $158/10^6$ population [1]. The annual incidence in the US has ranged across studies from 3 to $21/10^6$ population [2]. SSc is heterogeneous in terms of etiological factors, pathophysiology, clinical presentation, extent and severity of organ involvement, and immunoserological abnormalities. In the medium and long term, functional outcomes and mortality vary widely.

The evaluation of patients with SSc should include assessments of the severity of each organ involvement, of functional impairments, and of the impact on quality of life. This review focuses on laboratory tests that help to predict the prognosis of SSc. Some markers predict the overall prognosis, whereas others predict the risk of involvement of a specific organ (e.g. the lung, heart, kidney, gastrointestinal tract, or blood vessels).

2. Classification criteria for SSc

Although many classification schemes have been developed, all of them distinguish between limited cutaneous disease (lcSSc), in which the skin lesions do not extend beyond the elbows and knees but may involve the face, and diffuse cutaneous disease (dcSSc), which affects the thighs, arms, and torso. The preliminary criteria developed since 1980 by the American College of Rheumatology (ACR) [3] (Table 1) are

Table 1
Preliminary classification criteria for SSc [3]

I – Proximal skin scleroderma or two of the following three criteria
II – Sclerodactyly (fingers or toes)
Digital pittingscars / pulp loss
Bibasilar pulmonary fibrosis

E-mail address: olivier.meyer@bch.aphp.fr (O. Meyer).

1297-319X/$ - see front matter © 2006 Elsevier SAS. All rights reserved.
doi:10.1016/j.jbspin.2006.01.022

Table 2
Classification criteria for limited forms of SSc (from C. Leroy and Medsger [4])

A. Limited SSc
1. Documented Raynaud phenomenon
Clinical, with two of the three phases (pallor, cyanosis, erythema)
Or direct measurement of the response to cold (delayed color recovery or Nielsen test)
and 2. Or suggestive nailfold capillaroscopy findings (giant capillaries and/or decreased density)
Or presence of an autoantibody specific of SSc (anticentromere, anti-topoisomerase I, anti-fibrillarin, anti-PM/Scl, anti-fibrillin, anti-RNA polymerase I/III (titer > 1/100)
In patients with subjective symptoms of Raynaud phenomenon but no objective findings, both capillaroscopic and autoantibody criteria are required. Overlap syndromes are accepted
B. Limited cutaneous SSc
Same as A plus distal skin involvement beyond the elbows and knees. The face and neck may be involved (CREST is a synonym for limited cutaneous SSc)

ill-suited to early disease and to localized forms with no skin lesions beyond the fingers, no finger pad necrosis, and no interstitial lung disease (ILD). In 2001, LeRoy and Medsger [4] described a classification system for early SSc in which lcSSc is distinguished from limited SSc (lSSc) (Table 2). SSc-specific autoantibodies are taken into account in this system, which was developed using expert opinion as the reference standard. In a study of 152 patients with limited SSc, sensitivity was 92%, compared to only 33% for the ACR criteria. SSc sine scleroderma, in which no skin lesions develop, is classified with lcSSc. Of 555 patients studied by LeRoy and Medsger [4], 9% had SSc sine scleroderma. CREST syndrome (Thibierge–Weissenbach syndrome) is also classified with lcSSc.

Survival varies with the SSc subtype and classification criteria. In a study of 1166 patients included in the Pittsburgh Scleroderma Databank [5] between 1980 and 1989, 10-year survival was 69% in the group with lcSSc and 56% in that with dcSSc. More recently, a single-center study of 309 French Canadian patients found that 10-year survival rates in the limited, intermediate, and diffuse subtypes were 89%, 86%, and 62%, respectively, when only deaths directly related to SSc were considered ($P < 0.0001$) [6]. In a multicenter study of 1012 patients in Italy, 279 patients died, including 170 of known causes; SSc was the cause of death in 36% of cases and a possible cause of death in 52% [7]. Ten-year survival was 75.1% in patients with lcSSc and 53.4% in those with dcSSc ($P < 0.0001$) [7].

3. General prognostic markers

3.1. Erythrocyte sedimentation rate (ESR) and hemoglobin level

In multivariate analyses, ESR values equal to or greater than 15 mm/h and hemoglobin levels less than 12.5 g/dl were independently associated with death, the odds ratios (ORs) being 3.89 for ESR and 2.37 for hemoglobin. Both variables are independent from cutaneous involvement of the torso, which is an independent risk factor with a relative risk of 3.6 [6]. In earlier studies, a hemoglobin level less than 11 g/dl predicted death in multivariate models [8] and an ESR greater than 25 mm/h predicted death in multivariate [9] or univariate [7] analyses.

3.2. Antinuclear antibodies specific of SSc and prognosis

In 95% of patients with SSc, tests show antinuclear antibodies that are specific of SSc or of overlap syndromes with other connective tissue diseases. They are usually present at disease onset and persist throughout the course of the disease, albeit in fluctuating titers. Changes in specificity do not occur, so that antinuclear antibodies constitute reliable biological markers. Correlations have been shown between specific antibodies and specific features of SSc, some of which influence survival [10]. Actuarial survival curves differ according to the type of antibody. Less than 1% of patients have more than one SSc-specific antibody. Table 3 lists the main antinuclear antibodies and their associations with SSc subtype (limited or diffuse) and organ involvements [11]. Thus, anticentromere antibodies occur chiefly in lcSSc (including CREST syndrome), as do two less common antibodies, anti-7-2 RNP and anti-Th/To. In contrast, anti-topoisomerase I (Scl70) and anti-RNA polymerase III are associated with dcSSc. Anti-U1 RNP, Pm/Scl, and Ku usually occur in overlap syndromes that include lcSSc: thus anti-U1 RNP is associated with mixed connective tissue disease, anti-PmScl with polymyositis, and anti-Ku with lupus and polymyositis [12].

Several clinical manifestations are associated with specific antibodies. For instance, ILD is associated with anti-topoisomerase I; digital necrosis with anticentromere antibodies, delayed pulmonary hypertension (unrelated to ILD) with anticentromere antibodies, anti-U3 RNP/fibrillarin, and anti-Th/To; and renal crisis with anti-RNA polymerase III. Manifestations such as pulmonary hypertension, renal crisis, and ILD adversely affect survival, leading to differences in actuarial survival curves across patient subgroups defined based on antibody profiles. In a multicenter study of 1012 patients in Italy, 10-year actuarial survival was 72.2% in patients with and 80.8% in those without anti-topoisomerase I, 85.9% in patients with anticentromere antibody, and 72.6% in patients with antinucleolar antibody (U3 RNP, NOR 90, or PmScl) [7].

In a study by Steen [5] of 1432 patients in the Pittsburgh Scleroderma Databank, 10-year survival rates after the diagnosis of lcSSc was 88% in patients with anti-U1 RNP, 75% in those with anticentromere antibody, 72% in those with anti-PmScl, and 65% in those with anti-Th/To. In patients with dcSSc, 10-year actuarial survival was 64% with anti-topoisomerase I, 61% with anti-U3 RNP, and 75% with anti-RNA polymerase III [5]. A study of 275 patients managed in Japan between 1971 and 1990 showed that 10-year survival was 93% in patients with anticentromere antibodies, 72% with anti-U1 RNP, 66% with anti-topoisomerase I, and 30% with anti-RNA polymerase I [13].

Download English Version:

https://daneshyari.com/en/article/3367156

Download Persian Version:

https://daneshyari.com/article/3367156

Daneshyari.com