New Systemic Sclerosis Classification Created

BY BRUCE JANCIN
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KYOTO — One in five patients with clinical symptoms characteristic of systemic sclerosis do not fit into the popular classification scheme that divides the disease into the diffuse and limited cutaneous subtypes, according to Dr. Thomas Krieg.

This major limitation of the conventional bimodal classification system was among the key findings from the prospective German Network for Systemic Scleroderma registry, which includes 2,007 systemic sclerosis patients at 41 centers, Dr. Krieg said at an international investigative dermatology meeting.

The discovery that so many patients were excluded under the conventional two-subtype scheme prompted a joint committee of German dermatologists and rheumatologists who oversee the registry to create a new, more inclusive classification system by adding three more systemic sclerosis disease subtypes: overlap syndrome, undifferentiated scleroderma, and sclerosis sine scleroderma, explained Dr. Krieg, a dermatologist at the University of Cologne (Germany).

Overlap syndrome was defined as a disease featuring major symptoms of scleroderma simultaneously with those of other autoimmune diseases such as dermatomyositis, lupus erythematosus, or Sjögren's syndrome.

Sclerosis sine scleroderma consists of Raynaud's phenomenon, pulmonary arterial hypertension, and cardiac or gastrointestinal involvement in the absence of skin alterations.

Undifferentiated scleroderma was defined as Raynaud's phenomenon and at least one additional major feature of systemic sclerosis in patients not meeting the full American College of Rheumatology criteria.

Such features include nail-fold capillary changes, pulmonary hypertension, puffy fingers, or having scleroderma-specific autoantibodies.

Using the extended classification, 48% of the 2,007 patients have the limited cutaneous systemic sclerosis subtype, 31% have the diffuse cutaneous subtype, 11% have overlap syndrome, 8% have undifferentiated scleroderma, and less than 2% have sclerosis sine scleroderma, Dr. Krieg reported at the meeting of the European Society for Dermatological Research, the Japanese Society for Investigative Dermatology, and the Society for Investigative Dermatology.

The uniquely large and inclusive scleroderma registry has had surprising findings, said Dr. Krieg.

They include:

► A family history of rheumatic diseases, present in almost 20% of patients, was associated with a significantly younger age of scleroderma onset by nearly 3 years, along with a significantly earlier age at the onset of internal organ involvement. This suggests the importance of shared genes in the pathophysiology of a range of rheumatic diseases, according to Dr. Krieg.

► Patients who had overlap syndrome were more frequently managed by rheumatologists than dermatologists, but the nearly 80% of registry participants with the diffuse or limited cutaneous subtypes were seen equally by the two specialties.

► German patients with pulmonary hypertension, pulmonary fibrosis, digital ulcers, or conduction blocks were equally likely to be managed by dermatologists and rheumatologists; however, those with prominent gastrointestinal or musculoskeletal symptoms were more often cared for by rheumatologists.

► Despite a lack of published evidence that corticosteroids or immunosuppressive agents are effective in systemic sclerosis, Dr. Krieg said, 48% of patients treated by rheumatologists received steroids and 46% received immunosuppressive drugs, compared with 33% and 25%, respectively, of patients treated by dermatologists. Dr. Krieg said that he and his coworkers plan to pursue these specialty-based differences in treatment preferences by using them as the basis for controlled clinical trials.

► The female-to-male patient ratio varied from 3:1 to 7:1, depending upon systemic sclerosis subtype.

► Skin manifestations typically preceded internal organ involvement in all of the disease subsets. The length of time between the onset of Raynaud's phenomenon and the beginning of skin and internal organ involvement was shortest for the diffuse cutaneous scleroderma subgroup and longest for the limited cutaneous variant.

► The prevalence of joint contractures, creatine kinase elevation, diastolic dysfunction, arterial hypertension, sicca symptoms, pulmonary fibrosis, and stomach and intestinal involvement rose significantly within 1 year of follow-up. Rates of renal involvement and pulmonary hypertension remained stable.

► Of all the patients, 60% had esophageal involvement and 50% had musculoskeletal involvement. Pulmonary fibrosis was present in more than 33% of the patients, oral masticatory involvement in 25%, involvement with the heart in 15%, the stomach in 15%, and the kidneys in 10%.

► The specific organs involved varied according to disease subtype. Kidney, heart, and lung involvement were most common in the diffuse cutaneous subset. For example, the frequency of pulmonary fibrosis was 61% in the diffuse subgroup, compared with 31% in overlap syndrome and 24% in limited cutaneous systemic sclerosis. Musculoskeletal involvement was most common in overlap syndrome, with 69% of patients affected.

The systemic sclerosis registry is still ongoing.

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SSc Trend in Eastern Europe Not Explained by Geography

BY LEANNE SULLIVAN
Associate Editor

Patients who have severe manifestations of systemic sclerosis are seen more often in Eastern Europe than in other parts of Europe, according to a recent large database study.

However, referral bias precluded the identification of genetic or environmental factors contributing to the disease, wrote the authors.

Baseline data from the European League Against Rheumatism Scleroderma Trials and Research database were used to identify 3,661 systemic sclerosis (SSc) patients from a total of 61 European cities.

Of these, a total of 1,390 (38%) had diffuse systemic sclerosis and 2,263 (62%) had limited systemic sclerosis. The specific type of systemic sclerosis was unknown for just eight patients.

The mean age of all the patients was 55 years, and 87% were female, according to Dr. Ulrich A. Walker, of the department of rheumatology at the University of Basel (Switzerland), and his coauthors on the study.

Five of six cities had significant within-city differences in clinical subsets of SSc and two had significant differences in autoantibody prevalence.

In an attempt to identify genetic or environmental factors underlying the disease, the researchers analyzed data from 2004-2007 to discover whether there were any specific geographic differences in systemic sclerosis organ involvement as reflected by the presence of anticentromere autoantibodies and antitopoisomerase I (Scl-70).

The authors also looked for the existence of any geographic clusters of diffuse versus limited type of systemic sclerosis (Ann. Rheum. Dis. 2008 July 22 [doi:10.1136/ard.2008.091348]).

On bivariate analysis, no association was found between clinical subtype or autoantibodies and geographic location. However, one interesting finding was that there were more female patients with systemic sclerosis found in Western regions.

Additionally, Scl-70 was found more frequently in patients in Eastern Europe, the researchers said.

For partial correlations, data were adjusted for variables previously shown to determine particular organ manifestations, including autoantibody status, clinical subtype (either diffuse or limited), and the age at onset of Raynaud's phenomenon.

The association between female patients and Western European centers remained significant after adjustment for autoantibody status.

However, the link did not remain significant after subsequent adjustment for clinical subset.

"The highest correlation coefficient between disease presentations and geographical position was observed between diastolic dysfunction and longitude," Dr. Walker and his colleagues wrote.

However, because the centers that were near each other geographically did not have similar frequencies of diastolic dysfunction, the study authors hypothesized that "such differences may be attributed to observer-dependent differences in unstandardised echocardiographic assessment."

Cluster analysis was performed to determine if any features of systemic sclerosis were distributed in "pockets" rather than according to geographic longitude/latitude.

Within the six cities that had at least two centers with more than 15 SSc patients each (including Berlin, Madrid, Milan, Paris, Prague, and Lublin, in Poland), five of the locations showed significant within-city differences in clinical subsets and two places showed significant within-city differences in prevalence of autoantibodies. This particular finding reflected significant variation in systemic sclerosis presentation that was not explained by geographic factors.

Although geographic variations in systemic sclerosis prevalence and incidence have previously been described, variation in individual disease presentation had not been well studied, they said.

A previous study that was conducted in London found a higher prevalence of systemic sclerosis near airports.

There was also an Australian study that linked the disease with occupational exposure to silica dust.

However, the current cross-sectional study did not find a link between environment and systemic sclerosis.

The investigators also assessed referral bias by analyzing systemic sclerosis presentation and autoantibody status among centers located in the same cities or nearby.

The authors concluded that although "significant differences exist with regard to some disease presentations," there was "no clear geographical trend with regard to key factors."

The differences that were found to exist within cities and between those cities in close proximity are most likely explained by recruitment bias, the researchers continued.

Although the study "suggests that eastern European centres care for SSc patients with more severe manifestations than seen in other centres," the authors added that the evident "large local variability of SSc manifestations within adjacent centres suggests a substantial referral bias and precludes the identification of genetic or environmental factors."

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