Scleroderma Database Seeks to Gauge Organ Risk

Disease subset, antibody status, and age at onset of Raynaud's were all linked to organ manifestations.

BY NANCY WALSH
New York Bureau

The world's largest database on scleroderma, which now includes 5,500 patients from more than 100 centers on five continents, has begun to yield data that may more clearly delineate the evolution and variability of the disease and help assess risk for systemic organ involvement.

Currently, systemic sclerosis (SSc) is classified into diffuse cutaneous (dcSSc) and limited cutaneous (lcSSc) subsets according to degree and severity of skin involvement. This classification is inadequate, however, for predicting organ involvement, which is now crucial with the availability of targeted therapies that can alter outcomes, according to Dr. Ulrich A. Walker of the department of rheumatology, Basel University, Switzerland, and his colleagues.

With the goal of developing a more comprehensive disease classification system that better reflects the vascular, immunologic, and fibrotic processes that result in organ damage in SSc, the European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) database was formed in 2004. The group has now published its initial report, analyzing the association of various demographic, clinical, and laboratory factors with systemic organ involvement (Ann. Rheum. Dis. 2007 Feb. 1 [Epub doi:10.1136/ard.2006.062901]).

'The most important finding in this analysis was that antibody status is more predictive of individual disease presentation than is the disease subtype.'

At the data cutoff point for this first report in April 2006, 3,656 patients had been enrolled. A total of 1,349 (40%) were classified as dcSSc, with skin thickening extending proximal to the elbows and knees or with involvement of the trunk, and 2,101 (58%) as lcSSc, with skin involvement limited to the distal extremities and face.

The remaining 206 (6%) had scleroderma in combination with another connective tissue disease, according to the investigators. Among the SSc-associated autoantibodies detected were Scl70 autoantibodies in 1,330 patients and anticentromere autoantibodies (ACA) in 1,106, according to database findings reported by Dr. Walker and his associates.

Patients with dcSSc and those with lcSSc had the same mean age of onset of Raynaud's phenomenon, at 43 years, the investigators reported. The age of the first non-Raynaud's manifestation differed, however, being 45 years in dcSSc and 48 years in lcSSc. The mean modified Rodnan's skin score was 19 in the dcSSc group and 8.1 in the lcSSc group. Onset of disease was earlier in women, and early onset was associated with a decreased prevalence of severe organ involvement such as pulmonary fibrosis and pulmonary arterial hypertension, they noted.

Upon multivariate analysis, disease subset, antibody status, and age at onset of Raynaud's phenomenon all were independently associated with organ manifestations, but autoantibody status was associated with 15 organ manifestations and clinical subtype was associated with only 11 organ complications.

"The most important finding in this analysis was that antibody status is more predictive of individual disease presentation than is the disease subtype," said Dr. Walker in an interview.

Other findings that emerged from the analysis included the observation that 88.7% of patients who were positive for ACA had lcSSc, as did 36.1% of those who were anti-Scl70 positive.

Although there was no difference in mean age of onset of Raynaud's phenomenon between patients who were ACA positive and those who were anti-Scl70 positive, those with ACA had a longer mean lag period of 6.5 years before the onset of non-Raynaud's manifestations than did those with antiScl70, whose mean lag period was 2.4 years.

The database does not yet contain information on treatment and outcomes. This will be included when the database goes online, which is expected in approximately 6 months, Dr. Walker said.

The majority of participating clinics are in Europe, but three centers in the United States have enrolled patients, he added. ■

SLE Activity Predictive of Severity of Ischemic Stroke

BY MARY ANN MOON
Contributing Writer

Severe ischemic strokes are common in systemic lupus erythematosus patients, and a high level of disease activity predicts their occurrence, reported Dr. Jamal Mikdashi and his associates.

"The pathogenesis of ischemic stroke in SLE involves more than the traditional Framingham risk factors," but the features that predict stroke are not well understood in this patient population, the researchers wrote (Stroke 2007;38:281-85).

They studied predictive factors using data from the University of Maryland lupus cohort, in which 238 SLE patients were enrolled from 1992 to 2004 and were followed for a mean of 8 years. Of these subjects, 90% were women and 66% were black.

Ischemic strokes occurred in 44 patients (18%), and 34 of these (77%) were severe strokes, Dr. Mikdashi, of the University of Maryland, Baltimore, and his associates reported.

The most prevalent subtype was large-artery/atherothrombotic strokes (45%), followed by small-vessel/lacunar infarcts (39%). Seven patients (16%) had recurrent strokes during follow-up.

Baseline SLE activity, the presence of cutaneous vasculitis, and higher prednisone doses were significantly more frequent on univariate analysis in subjects who had a stroke than in those who did not have a stroke. On multivariate analysis, only high SLE activity predicted stroke.

When subjects were divided according to the severity of SLE activity at baseline, those with higher SLE activity scores were at twice the risk for ischemic stroke and at nearly three times the risk for severe ischemic stroke, compared with subjects with low SLE activity scores.

These findings suggest that besides conventional risk factors, "SLE patients may possess other characteristics that render them at greater risk for ischemic strokes," the investigators wrote.

Not surprisingly, hypercholesterolemia and hypertension also were found to be strong independent predictors of ischemic stroke. A substudy of statin therapy in this cohort indicated that it may reduce stroke risk.

"Further studies will determine whether treating hyperlipidemia and other traditional risk factors in SLE patients may substantially reduce or prevent the development of severe stroke and whether such measures will have impact on mortality, disability, and quality of life in SLE," Dr. Mikdashi and his associates noted. ■

Patients' Medical History Key to Neuropsychiatric Lupus Diagnosis

BY NANCY WALSH
New York Bureau

GLASGOW, SCOTLAND — Because the presenting symptoms of systemic lupus erythematosus are manifold, may mimic other disorders, and can evolve over time, assembling the diagnostic puzzle sometimes requires digging into the patient's past, according to Dr. Hala Y. Sadik.

This is particularly the case when the onset is acute, as happened in a case seen by Dr. Sadik of the University of Liverpool Academic Rheumatology Unit, University Hospital Aintree, Liverpool, England.

Careful review of history and investigation results is a necessity in any case where acute nonspecific symptoms might represent neuropsychiatric lupus.

In August 2005, a 57-year-old woman presented with hypothermia, bradycardia, confusion, a low score on the Glasgow coma scale, and hyponatremia. Plasma sodium was low, at 120 mmol/L; plasma osmolality was low, at 235 mosmol/kg; and urinary sodium and osmolality were high. The diagnosis of syndrome of inappropriate antidiuretic hormone secretion was made, Dr. Sadik wrote in a poster session at the annual meeting of the British Society for Rheumatology. Initial management included fluid restriction and administration of double-strength normal saline, which normalized the plasma sodium level.

Initial MRI of the head raised the possibility of neurosarcoidosis, but serum angiotensin-converting enzyme levels and chest x-ray were normal.

A repeat MRI with gadolinium suggested demyelinating disease or systemic lupus erythematosus. Immunology profile findings included positive antinuclear antibody (ANA) and double-stranded DNA antibody. Thrombocytopenia and lymphopenia also were present.

At this point, her previous case records were located at another hospital. These revealed that she had been admitted in 1992 with a 2-week history of arthralgias, Raynaud's phenomenon, thrombocytopenia, lymphopenia, and positive ANA.

A diagnosis of lupus had been considered at that time, and she was followed for several years as an outpatient, but ANA remained weakly positive and double-stranded DNA was persistently negative, so the diagnosis had been dismissed, Dr. Sadik wrote.

With improvements on the Glasgow coma scale during her current admission, it became apparent that the patient was profoundly depressed, so she was treated with mirtazapine. Following a diagnosis of neuropsychiatric lupus, she began treatment with intravenous methylprednisolone and cyclophosphamide.

Significant improvements were seen in her disabling depression, and her hematologic parameters normalized, according to Dr. Sadik.

This case highlights the necessity for careful review of medical history and investigation results in any case where acute nonspecific symptoms might represent neuropsychiatric lupus, she said. ■

Pages 20a—20d