ASK THE EXPERT

PAH in Connective Tissue Disease

Pulmonary arterial hypertension is a leading cause of morbidity and mortality in several connective tissue diseases, including systemic sclerosis and its cutaneous variant (CREST syndrome), systemic lupus erythematosus, and mixed connective tissue disease. Although the true prevalence of the condition among patients with connective tissue disease is unclear, reported estimates range from 12% to 30%.

CHRISTIAN M. KÄHLER, M.D.

In a landmark study investigating the point prevalence of diagnosed and undiagnosed pulmonary arterial hypertension (PAH) in more than 900 patients with systemic sclerosis or multiple connective tissue disease from 50 community rheumatology centers, 15% of the patients had a current PAH diagnosis, and an additional 13% had Doppler echocardiography results and early symptoms suggestive of the condition (Arthritis Rheum. 2005;52:2125-32).

Because the symptoms mimic those of numerous other lung problems, the condition frequently goes undiagnosed until its later stages or is misdiagnosed, according to Dr. Christian M. Kähler of the Medical University of Innsbruck, Austria. "In the early stages of mild to moderate disease, the symptoms [of PAH] are often misinterpreted as lack of fitness or cardiac ischemia. Later, more severe symptoms can mimic those of other lung conditions," Dr. Kähler said.

Unfortunately, the vagueness of the symptoms often precludes early diagnosis and aggressive treatment—both of which are critical for improving the odds of a good outcome, said Dr. Kähler. "There is currently no cure for [PAH], but there are agents that have been shown to slow its progression, especially if they are started early."

In this month's column, Dr. Kähler discusses the mechanisms of PAH in connective tissue diseases and offers insight into its clinical management.

Rheumatology News: What are the presumed mechanisms leading to PAH in patients with connective tissue disease?
Dr. Kähler: PAH is characterized by progressive obliteration of the small pulmonary vascular bed as a result of vascular proliferation and remodeling of the vessel wall leading to permanently increased pulmonary vascular resistance and elevated pulmonary artery pressures, which result in right heart failure and premature death. The pathologic processes of the condition in patients with connective tissue disease have been shown to be qualitatively similar to those seen in patients with idiopathic PAH. These include vasoconstrictor/vasodilator imbalance, thrombosis, misguided angiogenesis, and inflammation. In connective tissue disease, PAH may occur in association with interstitial fibrosis or it may occur in the absence of overt interstitial lung disease, possibly as a result of direct vascular involvement. Pulmonary vasospasm—the so-called pulmonary Raynaud's phenomenon—has been hypothesized as a potential contributor to the development of PAH in these patients, as has the possible association with antiendothelial cell and/or antifibroblast antibodies.

RN: What symptoms should treating rheumatologists be looking for?
Dr. Kähler: The key symptom in patients is unexplained dyspnea at exertion. Every patient with connective tissue disease suffering from dyspnea should be investigated for the underlying cause of symptoms, including presence of fibrosing alveolitis, pulmonary hypertension, or cardiac causes.

RN: What is the best test or procedure for detecting PAH?
Dr. Kähler: If there is a suspicion of the presence of PAH, a chest radiograph and a 2D echo Doppler echocardiogram should be considered as first-line diagnostic tools. The final diagnosis should be confirmed with right heart catheterization.

RN: What are the current treatments for PAH?
Dr. Kähler: Although there is as yet no cure for PAH, there are therapeutic options for controlling symptoms and slowing disease progression. Immunosuppressive therapy on its own seems ineffective, but in combination with prostacyclin they appear to help control and improve cardiac function. Also, endothelin receptor agonists and phosphodiesterase-5 inhibitors have been shown to reveal positive effects on symptoms, hemodynamics, and exercise capacity. Of course, early diagnosis and prompt consultation with the pulmonology service can optimize treatment efficacy. ■

DR. KÄHLER *is a member of the pneumology service within the division of internal medicine at the Medical University of Innsbruck, Austria.*

By Diana Mahoney, New England Bureau

Juvenile Systemic Sclerosis Diagnosis Hinges on Skin Signs

BY DIANA MAHONEY
New England Bureau

Evidence of proximal cutaneous sclerosis and at least 2 of 20 predefined minor criteria are required for a diagnosis of juvenile systemic sclerosis, according to new provisional classification criteria.

Using clinical data from real patients in combination with a consensus-based methodology, Dr. Francesco Zulian of the University of Padua (Italy) and colleagues on the Ad Hoc Committee on Classification Criteria for Juvenile Systemic Sclerosis—a combined effort of the Pediatric Rheumatology European Society, the American College of Rheumatology, and the European League Against Rheumatism—developed the new classification criteria to help standardize the conduct of clinical, epidemiologic, and outcome research for this rare pediatric disease and may alter patient care by enabling earlier, more definitive diagnoses (Arthritis Rheum. 2007;57:203-12).

The lack of standard classification criteria until now "has posed a barrier to the initiation of trials," according to Dr. Thomas J.A. Lehman of Cornell University, New York, who served on the classification committee. Clearly defined criteria are important for directing physicians who don't have much experience with the disease.

The much-needed juvenile criteria, which will supplant the adult criteria that have been used until now, "will help ensure that everyone included in a study has systemic sclerosis and not another condition or an overlap that may have a different long-term outcome," Dr. Lehman said in an interview. "For patient management, the criteria will help in convincing physicians that a patient does, in fact, have systemic sclerosis."

The criteria were developed in three phases, the first of which included the retrospective collection of information on demographic, clinical, and laboratory features of patients diagnosed with systemic sclerosis before age 16 from pediatric rheumatology centers worldwide. Investigators from the participating centers completed standardized case report forms to define organ involvement at the time of diagnosis. Forty-eight signs and symptoms, organized into nine categories were included for consideration.

In phase II, the committee developed questionnaires based on the data collected in phase I and sent them to 14 pediatric and adult rheumatologists with expertise in juvenile systemic sclerosis. The experts were asked to select the parameters essential for classification of the disease, based on their experience. Among the variables with the highest final scores, "those with a prevalence of at least 50% at the time of diagnosis, based on our patient population, were selected as provisional major criteria, and the remaining variables were listed as minor criteria," the authors explained.

In the third phase, the provisional criteria were evaluated by the same 14 experts in a consensus conference, using the clinical profiles of 160 actual patients with a variety of diagnoses, including 100 from patients with definite juvenile systemic sclerosis collected in phase I. A consensus of at least 80% of the experts was achieved for 127 of 160 patients, 70 of whom were judged as having the disease (all from the phase I group) and 57 as not having it. The 127 patients were then used as the accepted standard for rating the provisional classification criteria with the best statistical performance and highest face validity.

Of 86 different provisional classification criteria tested on the case profiles of the 127 patients, the criterion with the highest ranking was that which required the presence of proximal skin sclerosis/induration and at least 2 minor criteria, which is more restrictive than the adult classification criteria, according to the authors.

Conversely, the minor criteria in the proposed classification are more numerous than those used for adults.

Although validated with actual patient data, the new classification criteria must still undergo validation in external prospective trials, they noted. ■

Provisional Classification Criteria

Major criterion (Required)
- Proximal skin sclerosis/induration of the skin

Minor criteria
(At least two are required)
- Cutaneous
  - Sclerodactyly
- Peripheral vascular
  - Raynaud's phenomenon
  - Nailfold capillary abnormalities
  - Digital tip ulcers
- Gastrointestinal
  - Dysphagia
  - Gastroesophageal reflux
- Cardiac
  - Arrhythmias
  - Heart failure
- Renal
  - Renal crisis
  - New-onset arterial hypertension
- Respiratory
  - Pulmonary fibrosis (high-resolution computed tomography/radiography)
  - Decreased diffusing capacity for carbon monoxide
  - Pulmonary arterial hypertension
- Neurologic
  - Neuropathy
  - Carpal tunnel syndrome
- Musculoskeletal
  - Tendon friction rubs
  - Arthritis
  - Myositis
- Serologic
  - Antinuclear antibodies
  - Systemic sclerosis-selective autoantibodies

Source: Arthritis Rheum. 2007;57:203-12