Neuropsychiatric Issues Common in Early Lupus

BY SHARON WORCESTER
Southeast Bureau

DESTIN, FLA. — Neuropsychiatric manifestations of systemic lupus erythematosus occur in more than 80% of patients during the course of disease, and can pose challenges in caring for these patients.

Not only can such manifestations of lupus be difficult to distinguish from infectious or other nonimmunologically mediated processes, they can occur in the absence of serologic disease activity or other systemic manifestations, Dr. Robin L. Brey said at a rheumatology conference sponsored by Virginia Commonwealth University.

"The challenge to us in caring for patients complaining of some kind of neuropsychiatric manifestation … is really, first and foremost, determining if it is related to lupus," said Dr. Brey, professor of medicine and associate dean for research at the University of Texas Health Science Center, San Antonio.

The American College of Rheumatology has developed case definitions of several neuropsychiatric manifestations of lupus, including cerebrovascular disease, cognitive disorders, headaches, and movement disorders, among many others. Based on these case definitions, the prevalence of the manifestations in adults has been shown to be between 14% and 80%. Headaches, for example, occur in up to 61% of patients.

There is some controversy over whether headaches should be included in this list, as they are common both in lupus and nonlupus patients, but studies suggest that migraine with aura is especially likely to be a neuropsychiatric manifestation of lupus—a particular concern given the association between migraine with aura and increased stroke risk seen in some studies, and an important factor to evaluate for in general practice when treating lupus patients, Dr. Brey said.

Other lupus-related manifestations, according to the ACR case definition, include seizures, which occur in up to 18% of adults with lupus; cardiovascular disease, which occurs in up to 8% of adult patients; and psychosis, which occurs in up to 5% of adult patients. Cranial neuropathy and movement disorders occur only rarely—in about 2% and 1% of adult patients, respectively, Dr. Brey said.

Children with lupus have also been found to exhibit neuropsychiatric manifestations, and both children and adults tend to exhibit the manifestations early, she noted.

Studies show that between 28% and 40% of adults, and 11% of children, exhibit such manifestations at the time of lupus diagnosis, with up to 26% of children experiencing neuropsychiatric manifestations within 1 year of diagnosis.

Among the most common complaints are those associated with cognitive dysfunction. A subcortical pattern of complaints involving impairments in complex attention, cognitive processing speed, and memory retrieval is known as cognitive inefficiency, which can be very bothersome for patients and vexing for physicians to treat, she said.

This pattern is similar to that seen in HIV dementia, with a great deal more energy than normal required to perform cognitive functions. Some researchers believe this contributes to the fatigue experienced by many lupus patients, she noted.

Risk factors for the development of lupus-related cognitive dysfunction include Hispanic ethnicity, higher depression scores, higher damage scores and acute disease activity scores, consistent prednisone use, and persistently positive antiphospholipid and antiribosomal antibodies. Effects of neuropsychiatric manifestations may include decreased quality of life and increased lupus-related organ damage—both of which have been linked with these manifestations in adults.

Mortality may also be increased in those with these manifestations. In one study, the mortality rate over 20 years in children with lupus who experienced neuropsychiatric manifestations was 45%, compared with 17% in those without such manifestations.

As with the many other clinical manifestations of lupus, there are numerous possible causes. And given the varying manifestations, no single diagnostic test is sensitive or specific for identifying lupus-related neuropsychiatric manifestations, she added.

"Essentially, it takes an individualized approach, and it really, truly does depend on the complaint that the patient comes in with," she said.

Appropriate assessment for clinical care might include immunoserologic testing, brain imaging, and neurophysiological, psychiatric, and neuropsychological assessments, she said. However, infection must always be considered as a possible cause of the symptoms; lupus is not always to blame, she added.

Treatments are the same as those used to treat other serious lupus manifestations, and may include corticosteroids, azathioprine, cyclophosphamide, and mycophenolate mofetil. Symptomatic treatments—depending on the manifestation—may also be useful, such as for headaches, seizures, and stroke. ■

Insulin Resistance Differs in Rheumatoid Arthritis, Lupus

BY SHARON WORCESTER
Southeast Bureau

DESTIN, FLA. — The prevalence of metabolic syndrome is increased in patients with rheumatoid arthritis, compared with the general population, as is the prevalence of insulin resistance, data from numerous studies show.

Likewise, insulin resistance is increased in those with systemic lupus erythematosus, and the increased risks are independent of age, sex, race, body mass index, and corticosteroid use. These findings suggest that inflammation plays a role in the development of insulin resistance and other components of metabolic syndrome, although the mechanisms in the two diseases differ, Dr. C. Michael Stein reported at a rheumatology conference sponsored by Virginia Commonwealth University, Richmond.

For example, in a study in press at the time of Dr. Stein's presentation, the prevalence of insulin resistance was nearly 60% in patients with long-standing rheumatoid arthritis, and about 50% in those with early rheumatoid arthritis, compared with about 20% in controls. In a published study of lupus patients, more than 30% had insulin resistance, compared with about 11% of controls (Ann. Rheum. Dis. 2007; 66:208-14).

However, interleukin-6 levels have been shown to be significantly associated with insulin resistance in rheumatoid arthritis, (rho 0.63; *P* less than.001), but not in lupus (rho 0.16; $P = .18$), and the same has been shown to be true for tumor necrosis factor–α (rho 0.50; *P* less than .001and rho 0.11; $P = .24$, respectively), said Dr. Stein of Vanderbilt University, Nashville, Tenn.

Body mass index traditionally is an important factor in the metabolic syndrome pathway to coronary heart disease, and was significantly associated with insulin resistance in lupus in the study (rho 0.54; *P* less than .001), but it appears that inflammation also can lead to the same pathway, he explained.

In addition, atherosclerosis is accelerated in both diseases. This also may be a factor of inflammation, as well as of insulin resistance and metabolic syndrome. It does not appear, in these diseases, to be associated with traditional cholesterol/lipid concentration–related mechanisms, Dr. Stein noted.

"The good news is that the features of metabolic syndrome can be reversed," he said.

The same lifestyle interventions recommended for other patients with metabolic syndrome are recommended for those with rheumatoid arthritis or lupus. As for the potential for treatments that target the inflammatory mediators of these diseases to have a beneficial effect on insulin resistance and metabolic syndrome, he said, research is underway. ■

Belimumab Is Steroid Sparing in Systemic Lupus Erythematosus

BY NANCY WALSH
New York Bureau

PARIS — Treatment of patients with systemic lupus erythematosus with the monoclonal antibody belimumab permitted reductions in corticosteroids through 3 years of observation, according to a post hoc analysis of a large phase II study.

Treatment options for lupus are limited, and most are associated with significant adverse effects.

DR. WALLACE

Treatment options for systemic lupus erythematosus (SLE) are limited, and most of the available options are associated with significant and even debilitating adverse effects. Corticosteroids, for example, are associated with weight gain, risk of infection, psychosis, and hypertension and so generally are reserved for use during times of disease activity. An agent that could be steroid sparing remains a critical unmet need in the SLE treatment regimen, according to Dr. Daniel J. Wallace of Cedars-Sinai Medical Center, University of California, Los Angeles.

Belimumab targets and inhibits soluble B-lymphocyte stimulator (BLyS), a protein that is overexpressed in SLE.

Following the completion of a double-blind trial, patients were allowed to enroll in an open-label extension trial in which they received 10 mg/kg of belimumab monthly. A total of 296 participants chose to continue in the study and 233 remained enrolled at the time of Dr. Wallace's EULAR presentation.

At baseline, the majority of patients were women whose mean age was 42 years. Mean disease duration was 8.8 years, and most patients had a reduction in disease activity as measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) as modified for the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA).

A total of 69% were on daily prednisone, with a mean dose of 11 mg/day, and 36% were on doses higher than 7.5 mg/day.

At the end of the randomized phase, reductions in average prednisone dose to 7.5 mg/day or lower were seen in 34%, 28%, 31%, and 44% of patients in the placebo, 1-mg/kg, 4-mg/kg, and 10-mg/kg groups, while increases from low-dose prednisone to doses of 7.5 mg/day or higher were needed in 17%, 11%, 10%, and 4%, respectively.

At the end of year 3, when patients from all groups were on the highest dose of active treatment, prednisone reductions were seen in 56%, 45%, 61%, and 62% of patients originally in the placebo, 1-mg/kg, 4-mg/kg, and 10-mg/kg groups, and increases were seen in 8%, 5%, 12%, and 7%, respectively.

Dr. Wallace has declared no conflicts of interest. ■