Longevity Raises New Issues

Lupus *from page 1*

rheumatology, Hospital for Special Surgery, and professor of clinical pediatrics, Cornell University, both in New York.

Dr. Lehman treated 12 patients with active systemic lupus erythematosus (SLE), whose median age was 14 years, with intravenous infusions of rituximab in doses of 600 mg/m^2 followed by cyclophosphamide, 750 mg/m^2, over a 2-week period, and with repeat infusions at 6 months.

All patients had significant clinical improvements on their disease activity scores. Laboratory parameters also improved, with increases in C3 and decreases in erythrocyte sedimentation rate. Hemoglobin, white blood cell count, IgG, and IgM remained stable, and there were no serious adverse events.

"This more intensive early therapy seems to have better results, and we are hoping it won't be necessary to continue treatment indefinitely, but it's still early. We need longer-term follow-up and controlled trials to determine the optimal treatment regimen and identify possible late-onset side effects," Dr. Lehman cautioned.

Dr. Abitbol also has a large cohort of pediatric lupus patients in Miami, most of whom are Hispanic or African American and have stage IV or V nephritis. At present, 18 have been treated with rituximab, administered weekly for two to four doses. The initial dose used was 188 mg/m^2, and subsequent doses were 375 mg/m^2.

Mean age at diagnosis of SLE in these patients was 11 years, and mean disease duration before treatment with rituximab was 3 years. Sixteen had either failed on cyclophosphamide plus corticosteroids or experienced toxicities. Three patients were on dialysis at the time of treatment. All three improved; one ultimately received a transplant and the other two have remained stable and continue on dialysis. Of the other 15 patients, all with active lupus nephritis and significant proteinuria, 7 had complete remission of their proteinuria, and 7 had partial remission. Treatment with rituximab also permitted reductions in corticosteroids from an average of 79 mg/m^2 per day before rituximab to 13 mg/m^2 (Pediatr. Nephrol. 2008;23:413-9).

"We can use rituximab judiciously as an adjunctive therapy to try to spare the more toxic medications, particularly Cytoxan," Dr. Abitbol said in an interview.

Most adverse events in this cohort were mild and infusion-related, including nausea, pruritis, and malaise. One patient died from overwhelming *Staphylococcus aureus* infection associated with severe immunosuppression, possibly relating to previous treatment with cyclophosphamide.

"We stopped using Cytoxan with rituximab after this," she said.

Safety concerns were more prominent in a retrospective study by the French Pediatric-Onset SLE Study Group, in which 11 girls with severe lupus received 2-12 intravenous infusions of rituximab in doses of 350-450 mg/m^2. Six also received standard immunosuppressive agents. Remission was achieved in eight patients. Severe adverse events, including septicemia, thrombocytopenia, and neutropenia, occurred in five patients who also were taking immunosuppressants (J. Pediatr. 2006;148:623-7).

An editorial accompanying this report offered a reminder about differences in adult and pediatric lupus. "Despite similarities in the clinical features of adults and children with SLE, subtle immunologic differences between adults and children have long been recognized, and these differences may also be important when using rituximab treatment." They also noted that children have higher numbers of pregerminal center CD38++ B cells, which tend to be more resistant to depletion with rituximab than other B cells (J. Pediatrics 2006;148:571-3).

Dr. Abitbol also described new challenges being faced by young patients as they live longer. "We weren't following patients for 10-15 years in the past, because they didn't survive," she said. Now patients must adhere to long-term maintenance therapy and make the transition to adult care. Pregnancy also can complicate the picture, said Dr. Abitbol. "We had one lupus patient who was very obese and didn't realize she was pregnant. She continued taking her angiotensin blocker for hypertension, and her child, who is now 7 [years], is on dialysis because those drugs interfere with kidney development in the fetus," she said.

Low bone mineral density is another prevalent problem, even in these young patients. In one study from the Hospital for Sick Children in Toronto that included 64 patients whose disease had been diagnosed before age 18, lumbar spine osteopenia was seen in 24 patients and osteoporosis in 13 (Arthritis Rheum. 2007;56:1966-73).

In an interview, Dr. Lehman explained that bone loss can be minimized by avoiding excessive steroids, which is one of the advantages of using rituximab and steroid-sparing agents like mycophenolate mofetil.

Dr. Lehman and Dr. Abitbol declared that they have no financial conflicts. ■

Lysosomal Storage Disorders: Awareness, Early Action Are Key

BY DIANA MAHONEY
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An awareness of lysosomal storage disorders as a cause of joint abnormalities in children is essential for identifying the genetic disorders and intervening before permanent musculoskeletal damage occurs.

"New therapies are available, but their effect on bone and connective tissue disease is slow, so they need to be applied early for maximal benefit," Dr. J. Edmund Wraith said at the annual congress of the Paediatric Rheumatology European Society.

Lysosomal storage diseases (LSDs) are heterogenous, inherited disorders characterized by the absence or deficiency of specific enzymes involved in the breakdown of macromolecules within the lysosomes of human cells. The resulting cellular dysfunction leads to progressive physical and/or mental deterioration, and death in some cases.

"There are a number of classic presentations, including hydrops fetalis; enlargement of the liver and spleen; neurodegenerative disease; and, most relevant to rheumatologists, skeletal dysplasia known as dyostosis multiplex and connective tissue involvement leading to progressive joint stiffness," said Dr. Wraith of the Royal Manchester (England) Children's Hospital. "The disorders most often seen by rheumatologists are the attenuated form of mucopolysaccharidosis type I [Hurler/Scheie and Scheie disease], [and] mucolipidosis type III [pseudo-Hurler polydystrophy], in which skeletal involvement is prominent."

These conditions, as well as two additional storage diseases—Gaucher disease, caused by a glucocerebrosidase deficiency, and Fabry disease, caused by deficiency of α-galactosidase A—can lead to musculoskeletal symptoms that can be mistaken for rheumatoid diseases. Patients with attenuated phenotypes of the mucopolysaccharidosis type I (MPS-I) disorders, for example, "often present during the first decade of life with joint contractures or a decreased range of motion, which can easily be mistaken for some form of juvenile arthritis," said Dr. Hartmut Michels of the Rheumatic Children's Hospital, Garmisch-Partenkirchen, Germany. The skeletal complications of Gaucher disease type I, which include polyarthralgia of large peripheral joints, widening of the distal femur, bone pain, and bone crisis accompanied by swelling, localized skin erythema, and a raised erythrocyte sedimentation rate "can lead to a misdiagnosis of acute arthritis if the bone crisis is located close to a joint."

The musculoskeletal symptoms of some of the other LSDs include a progressive restriction of joint mobility in the early years of life in mucolipidosis type III, and generalized pain and pain attacks similar to those seen in systemic vasculitides, connective tissue disease, or pain syndromes in Fabry disease, Dr. Michels noted.

'Family histories revealed that 92% [out of 1,555 patients] had additional family members suffering from Fabry disease,' making history taking crucial.

While the early musculoskeletal symptoms may mimic rheumatoid conditions, the full clinical picture often tells a different story, said Dr. Wraith. For example, in the autosomal recessive MPS-I disorders, the characteristic bone and soft tissue changes "are usually not accompanied by the swelling and redness of the joints that are seen in the inflammatory arthropathies. Also, stiffness rather than pain tends to be the primary symptom," he said.

Anti-CCP antibodies or antinuclear antibodies, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are typically not present in the storage diseases, said Dr. Michels. "Gaucher disease type I is an exception, because ESR may be elevated and antinuclear antibodies may be detected." Prominent features of Gaucher disease type I include marked hepatomegaly and splenomegaly.

The nonspecific nature of early Fabry disease in children makes it one of the more difficult LSDs to diagnose, and a misdiagnosis of this X-linked sphingolipidosis can have the most devastating consequences, according to Dr. Michels. Caused by a systemic overaccumulation of globotriaosylceramide and related glycosphingolipids in lysosomes through the body, Fabry disease is characterized by progressive tissue and organ damage and ultimate organ failure. It affects, in particular, the kidneys, cardiovascular system, and cerebrovascular system.

Although the early, nonspecific symptoms, such as generalized pain and heat and cold intolerance, can easily be mistaken for fibromyalgia or a systemic vasculitide, "a thoroughly performed family history is important in obtaining an early diagnosis," Dr. Michels and his colleagues observed in a recent review article. In one evaluation, they wrote, "Family histories revealed that 92% [out of 1,555 patients] had additional family members suffering from Fabry disease, comparable to the results of another study which demonstrated 43% of pediatric patients whose correct diagnosis was reached through their family histories," (Curr. Opin. Rheumatol. Jan. 2008 [20]:76-81).

An awareness of the typical clinical picture of the relevant LSDs is essential, said Dr. Michels. "For example, hepatosplenomegaly in a child assumed to have oligoarticular juvenile idiopathic arthritis probably indicates Gaucher disease type I; carpel tunnel syndrome in a child thought to have JIA could be a symptom of MPS I-Scheie; and a stroke in a young adult with symptoms of fibromyalgia could mean Fabry disease," he said. When an LSD is suspected, laboratory tests including lysosomal enzyme assays, can unequivocally diagnose or exclude the relevant disorders, he said.

"Until recently, rheumatologists did not have storage diseases on their differential diagnostic menu because the diseases were rare and not treatable," said Dr. Bernhard Manger of the University of Erlangen-Nuremberg, Germany. "Now there is no excuse. ... There are treatments."

Enzyme replacement therapy via intravenous injection of recombinant proteins is the most common, Dr. Wraith said. The intravenous infusion of recombinant proteins effectively slows disease progression; thus, optimal efficacy requires early intervention, he said. The treatment is not a cure, however, and must be continued for life.

Other strategies include substrate reduction therapy and chemical chaperone therapy, which involve the application of small molecules that either inhibit the enzyme responsible for substrate synthesis or act as a chaperone to increase the residual activity of the lysosomal enzyme, said Dr. Michael Beck of the University of Mainz (Germany). In addition, "various in vivo and ex vivo gene therapeutic techniques have been developed, but are not yet available," he said. "[These] administer the gene that is defective in a patient to the bloodstream or directly to the brain in order to overcome the blood-brain barrier." ■