**Lysosomal Storage Disorders: Awareness, Early Action Are Key**

**BY DIANA MAHONEY**
New England Bureau

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 heterogeneous, inherited disorders characterized by the absence or deficiency of specific enzymes involved in the breakdown of macro-molecules 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 dystrophy multisystemica 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 glucose cerebroside 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 (Hurler/Scheie disease) who develop the full clinical picture, "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 mucopolysaccharidosis type III, and generalized pain and pain attacks similar to those seen in systemic vasculitis, connective tissue diseases, or pain syndromes in Fabry disease, Dr. Michels noted.

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 blood cells, cells of the monocyte/macrophage system, and all cell types, Fabry disease presents with 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 vasculitis, “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 LSDs is essential, said Dr. Michels. "For example, heptosplenomegaly in a child assumed to have oligoarticular juvenile idiopathic arthritis may turn out to be Fabry 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 disease in their differential diagnoses 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 chemical agents that bind 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."