Scientists discover new genetic immune disorder in children

June 4 2009

Your immune system plays an important function in your health—it protects you against viruses, bacteria, and other toxins that can cause disease. In autoinflammatory diseases, however, the immune system goes awry, causing unprovoked and dangerous inflammation. Now, researchers from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), part of the National Institutes of Health, and other institutions have discovered a new autoinflammatory syndrome, a rare genetic condition that affects children around the time of birth. The findings appear in the current issue of the *New England Journal of Medicine*.

The scientists have termed the new autoinflammatory syndrome DIRA (deficiency of the interleukin-1 receptor antagonist). Children with the disorder display a constellation of serious and potentially fatal symptoms that include swelling of bone tissue; bone pain and deformity; inflammation of the periosteum (a layer of connective tissue around bone); and a rash that can span from small individual pustules to extensive pustulosis that covers most of the patient's body. Most of the children begin to have symptoms from birth to 2 weeks of age.

"The beauty of this discovery is that the symptoms of this devastating disease can now be treated," said NIAMS director and immunodermatologist, Stephen I. Katz, M.D., Ph.D. "The abnormal inflammatory pathways seen in this disease may also help us understand other common diseases that share clinical features, such as psoriasis, as well as other autoinflammatory disorders."

"We knew when we saw these children that we were dealing with a previously unrecognized autoinflammatory syndrome. The clinical characteristics were distinct from other diseases we had seen before," said NIAMS researcher and lead author Raphaela Goldbach-Mansky, M.D., M.H.S. When her colleague, Dr. Ivona Aksentijevich, tested the first patient for genetic abnormalities, their suspicions were confirmed, and ultimately abnormalities were found in a number of other cases.

All the children had inherited mutations in IL1RN, a gene that encodes a protein known as interleukin-1 receptor antagonist (IL-1Ra). IL-1Ra binds to the same cell receptors as the inflammatory protein interleukin-1, and acts as a brake on this inflammatory protein. Without IL-1Ra, the children's bodies cannot control systemic inflammation that can be caused by interleukin-1.

The scientists identified nine patients from six families with DIRA in the Canadian province of Newfoundland, the Netherlands, Lebanon, and Puerto Rico. Those who were alive at the time of diagnosis—six in all—were treated with anakinra, a drug that is normally used for rheumatoid arthritis and is a synthetic form of human IL-1Ra. Although the patients were resistant to other medications such as steroids, most responded successfully and immediately to anakinra. "Our first patient had been unresponsive to several treatments, and his health care team had almost given up. But with anakinra, he was out of the hospital in 10 days and his symptoms resolved," Dr. Goldbach-Mansky said.

Although the mutation that causes DIRA is rare, as many as 2.5 percent of the population of northwest Puerto Rico are carriers. Since DIRA is recessively inherited, these data suggest that it may be present in about 1 in 6,300 births in this population. Because the mutation was found in three independent Dutch families, newborn screening for DIRA in this population, as well as that of northwest Puerto Rico, may be warranted, Dr. Goldbach-Mansky said.

"The DIRA discovery can be attributed to an innovative and collaborative effort between clinicians and laboratory researchers at NIAMS and an international team of dedicated investigators," said NIAMS Clinical Director and coauthor Daniel L. Kastner, M.D., Ph.D. "Moreover, the unveiling of this novel autoinflammatory syndrome provides us with a tool to further dissect the role of interleukin-1 in human biology and disease."

More information: Aksentijevich I, Masters SL, Ferguson PJ, et al. An autoinflammatory disease with deficiency of the interleukin-1 receptor antagonist. *N Engl J Med* 2009;360:2416-27.

Source: National Institute of Arthritis and Musculoskeletal and Skin Diseases