Premature aging of immune cells in joints of kids with chronic arthritis

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The joints of children with the most common form of chronic inflammatory arthritis contain immune cells that resemble those of 90-year-olds, according to a new study led by researchers at Children's Hospital of Pittsburgh of UPMC and the University of Pittsburgh School of Medicine. The findings, published in the August issue of *Arthritis and Rheumatism*, suggest that innovative treatment approaches could aim to prevent premature aging of immune cells.

Juvenile idiopathic arthritis, or JIA, is the most prevalent rheumatic condition in the world and affects one of every 1,000 children in the U.S., said senior researcher Abbe de Vallejo, Ph.D., associate professor of pediatrics and immunology, Pitt School of Medicine. It usually starts with a swollen ankle, knee or wrist that parents often assume is due to a minor injury sustained while playing.

"Untreated JIA has devastating consequences," Dr. de Vallejo said. "It can slow growth and, in extreme cases, the child can be physically disfigured. It's a degenerative disease that eats up the joints."

Doctors have long thought of JIA as an autoimmune disease, meaning the body attacks itself. But previous studies by Dr. de Vallejo of young adults with rheumatoid arthritis indicated that a certain population of cells present in the joint synovial fluid and blood displayed telltale signs of abnormal cell division and premature aging. His current team at Children's wanted to see if that was true in pediatric arthritis.

They examined immune cells called T-cells in the synovial fluid and blood from 98 children ages 1 to 17 and known to have JIA, as well as 46 blood samples from children who didn't have the disease. T-cells are the army of immune cells that eradicate infection, tumors and other dangerous agents to which people may be exposed.

The research team found about one-third of the T-cells of children with JIA had shortened telomeres and had reduced, or in some cases lost, the capacity to proliferate. Telomeres are the ends of chromosomes that don't code for proteins and, because they are not fully copied by enzyme mechanisms, are trimmed slightly during each DNA replication cycle. It is thought that aging occurs when the telomeres become too short for DNA replication and cell division to proceed normally.

"The T-cells of the children with JIA had very short telomeres, about the length we see in a 90-year-old or a young adult with rheumatoid arthritis. Those same T-cells express unusually high levels of several classic protein markers of cell aging and exhaustion," Dr. de Vallejo said. "These kids haven't lived long enough to have cells that look that old. This is the first indication that premature aging in occurring in this childhood condition."

In addition, the T-cells had become dysregulated, and their immune activity could be stimulated through atypical cell surface receptors. Much more must be learned about the unusual cells and about genetic mechanisms that might contribute to the development of JIA, Dr. de Vallejo said, but these findings could point the way to new therapies.

"JIA is typically treated with broad-spectrum drugs such as steroids and biologics that essentially paralyze the entire immune system, but only a third of the cells are affected and their abnormality seems to be premature aging, rather than autoimmune activity," he noted. "This study suggests cell-targeted treatments could be developed to prevent this

premature immune aging."

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