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Protein that triggers juvenile arthritis identified

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Juvenile idiopathic arthritis, or JIA, is the most common form of childhood arthritis. It appears to be an autoimmune disease, caused by antibodies attacking certain proteins in a person's own tissue. But no "autoantigens"—the proteins triggering an immune attack—have been linked to JIA.

Now, a new study offers evidence that a human protein called transthyretin (TTR) causes an autoimmune reaction in the joints of JIA patients. The study, led by researchers at Albert Einstein College of Medicine and the Children's Hospital at Montefiore (CHAM), was published online today in the journal *JCI Insight*.

"Our findings regarding TTR's involvement in JIA point to a potential treatment—encouraging news for children with this debilitating disease," said study leader Laura Santambrogio, M.D., Ph.D., professor of pathology, of microbiology & immunology, and of orthopaedic surgery at Einstein. JIA patients, she says, might benefit from a drug called tafamidis, which targets TTR. Tafamidis was approved in Europe and Japan for treating familial amyloidosis, which is also linked to TTR. The drug is now undergoing phase III trials in the U.S.

JIA affects about 300,000 children in the U.S. Symptoms include chronic joint pain, swelling and stiffness, which may persist for a few months or a lifetime. There is no cure. Treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs) and biologic response modifiers are used to control symptoms and prevent complications.

In the current study, Dr. Santambrogio and her colleagues looked for abnormal accumulations of proteins in the synovial fluid (which bathes the joints) and blood of patients with JIA. They found a significant increase in TTR in 50 patients at the Children's Hospital at Montefiore, but not in any of the 26 control children who did not have JIA. Further analysis revealed that some JIA patients had unusually high levels of antibodies to the TTR protein. To validate this finding, the researcher analyzed 43 other JIA patients and found a significant increase in TTR autoantibodies in all of them.

TTR is a molecular "chaperone" that transports various molecules, including thyroxine and retinol (vitamin A), in the blood and cerebral spinal fluid. The researchers suspect that JIA begins when TTR collects in the joints.

"The TTR protein has a tendency to misfold and then aggregate, which for some reason seems to occur in children with JIA," said Dr. Santambrogio. "And when proteins aggregate, they tend to become more immunogenic." Using mass spectrometry and other biophysical techniques, the researchers observed misfolded and aggregated TTR in the synovial fluid of JIA patients. The patients' TTR protein was also heavily oxidized, which may further increase its immunogenicity. When abnormal TTR was administered to mice, it elicited a higher immunogenic response (i.e., caused more antibodies to be produced) compared to normal TTR.

The paper is titled "Autoimmune Response to Transthyretin in Juvenile Idiopathic Arthritis."

More information: Cristina C. Clement et al. Autoimmune response to transthyretin in juvenile idiopathic arthritis, *JCI Insight* (2016). DOI: 10.1172/jci.insight.85633

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