Scientists discover link among spectrum of childhood diseases

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An international collaboration of scientists, including researchers at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), a part of the National Institutes of Health, has identified a genetic mutation that causes a rare childhood disease characterized predominantly by inflammation and fat loss. The research suggests that the disorder, named chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), actually represents a spectrum of diseases that have been described in the literature under a variety of names. More importantly, since no effective treatment for this disease currently exists, the findings may have uncovered a possible target for future treatments.

The collaboration began when NIAMS rheumatologist Raphaela Goldbach-Mansky, M.D., started seeking the cause of inflammatory skin lesions, fat loss and fevers in two of her young patients. At a scientific meeting, she learned about recent publications by two other research groups — one led by dermatologists Antonio Torrelo, M.D., from the Boy Jesus Hospital, Madrid, and Amy Paller, M.D., from Northwestern University, Chicago, and the other led by Abraham Zlotogorski, M.D., from the Hadassah-Hebrew University Medical Center, Jerusalem — describing similar conditions. She immediately located the publications' authors and emailed them that same night.

"It turned out they had found each other and were looking for a genetic cause and additional cases," said Dr. Goldbach-Mansky. "I contacted them with a case report with pictures and they sent me theirs."

Based on the clinical presentation and, particularly, the unusual skin lesions seen in the children, the researchers suspected that the children must have the same disease. Subsequent analyses — involving biopsies, blood tests and genetic testing — confirmed their suspicions. All but one child had at least one mutation in a gene called PSMB8, which had been recently identified in three adult patients with a disease called joint contractures, muscle atrophy and panniculitis-associated lipodystrophy (JMP).

PSMB8 is one of more than 20 components involved in making a cellular structure called a proteasome, which recycles proteins from cells that are stressed or dying.

"When the proteasome doesn't function, there is a buildup of protein waste products in the cells — much like if your trash wasn't picked up each week, it would accumulate in your driveway," said Dr. Goldbach-Mansky.

The one patient without the mutation had a blood profile that was identical to the ones who did, and showed the same accumulation of waste products in the cells seen in children with the genetic mutation. Blood tests also showed high levels of an inflammatory chemical called interferon gamma-induced protein 10 (IP-10) that is stimulated by interferons. The chemical is produced in response to some infections, and the group suspects that it also may be produced in the cellular stress response.

The discovery, which is described in Arthritis *& Rheumatism*, unifies several different diseases into one spectrum of proteasome-associated autoinflammatory syndromes, said Dr. Goldbach-Mansky. She hopes that these findings will enable doctors to identify more children who fit into this spectrum of difficult-to-treat disorders so that they can develop a better understanding of the disorders and their treatment.

Despite the best treatments currently available — which, in most cases, consist of high doses of steroids — children with these disorders continue to lose fat and suffer metabolic changes that lead to a range of problems, including loss of muscle mass, dilated heart muscles and cardiac arrhythmias. Treatments for other inflammatory diseases have little, if any, effect on the prognoses of these diseases. The group's findings, however, suggest new therapeutic targets.

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