Research shows genetic anti-inflammatory defect predisposes children to lymphoma

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New research shows that children with an inherited genetic defect in a critical anti-inflammatory pathway have a genetic predisposition to lymphoma. Results of the study, published online today in *Blood*, the Journal of the American Society of Hematology (ASH), reveal an important association between the genetic defect, which causes chronic intestinal inflammation and early onset inflammatory bowel disease, and its role in cancer development in infants and children.

Among the hundreds of signaling pathways in the human immune system that guide the body's defense against infection, inflammation, and trauma, the interleukin-10 (IL-10) pathway plays a substantial role in regulating and safeguarding the intestinal tract. In rare cases, a genetic defect can appear in the IL-10 or in one of its receptors (IL-10R1 and IL-10R2) that turns off the pathway's normal protective function, resulting in the development of very-early-onset inflammatory bowel diseases (VEO-IBD) in children as young as two weeks old.

While chronic intestinal inflammation is a known risk factor for cancer, until this study no formal connection had been made between IL-10 deficiency, VEO-IBD, and the development of certain malignancies. Researchers began to investigate this potential linkage when five children between 5.5 and 6.5 years of age being monitored for VEO-IBD at the Necker Children's Hospital in Paris and the Munich Children's Hospital developed highly proliferative and severe cancer very similar to diffuse large B-cell lymphoma (DLBCL), an extremely rare form of blood cancer in children.

"When one VEO-IBD patient with an IL-10R deficiency developed diffuse large B-cell lymphoma, we suspected it might be an unfortunate circumstance. However, when the second, third, fourth, and fifth child were diagnosed, it was clear that this was not a chance occurrence," said lead study author Alain Fischer, MD, PhD, of the Imagine Institute, French National Institute of Health and Medical Research and Assistance Publique – Hôpitaux de Paris in Paris.

To explore the subset and type of the children's lymphomas, investigators performed several analyses to characterize their molecular composition, identify chromosomal abnormalities, and examine their genetic expression profiles. Following these analyses, the research team observed that all five children exhibited sub-types of DLBCL so extraordinarily similar that the similarity could not be atrributed to random occurrence, but rather reflected consequences of the defective IL-10 pathway.

In confirming their discovery, researchers considered that the predisposition to lymphoma in the five children with IL-10 deficiency could have been related to the immunosuppressive therapy that four of them received for VEO-IBD. However, of the 53 children being monitored at the Necker Children's Hospital and the Munich Children's Hospital for VEO-IBD who received the same therapy, the children with IL-10 deficiency were the only ones who developed lymphoma.

While this finding confirms an association between a nonfunctioning IL-10 pathway and lymphoma, the mechanism by which this genetic deficiency activates cancer development has not yet been identified. One hypothesis considers the IL-10 pathway's role in regulating the proliferation of B cells in the body and proposes that an IL-10 deficiency may lead to uncontrolled cell activity and ultimately cancer. Another potential explanation contends that IL-10 deficiency may impair the disease-fighting ability of local T cells, a type of white blood cell.

Given the established protective effects of the IL-10 pathway and the elevated risk of lymphoma observed in these IL-10-deficient children, these findings may lead researchers to develop a more complete understanding of how the IL-10 pathway may be manipulated to aid in cancer prevention.

"The confirmed association between the IL-10 pathway and this rare pediatric lymphoma provides a valuable tool to predict cancer risk in children with VEO-IBD so that doctors can take preventive action that may prevent the occurrence or reoccurrence of lymphoma," said Dr. Fischer.

Provided by American Society of Hematology