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WHIM Syndrome: A Misguided Immune System!

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Newburger:
Hello. I'm Dr. Peter Newburger. I'm Professor of Pediatrics and Molecular, Cell and Cancer Biology at UMass Chan Medical School, as well as an Attending in Hematology at Boston Children's Hospital. I'm speaking today about WHIM syndrome, a disorder representing a misguided immune system.

WHIM syndrome is due to gain of function mutations in the CXCR4 receptor. This receptor, upon binding its ligands, primarily CXCL12, triggers multiple signaling pathways that orchestrate cell migration, hematopoiesis, cell homing, and retention in the bone marrow. This figure shows multiple pathways that are impacted by CXCR4 activation.

The mutations in CXCR4 occur in the cytoplasmic tail, shown with the dashed red lines in this schematic. This is the site of binding of beta-arrestin, which terminates signaling by bringing about internalization of the receptor and degradation in lysosomes. When that cytoplasmic tail is missing due to truncation mutations, there's impaired internalization of the receptor, so receptor internalization and degradation do not occur, and hyperactive signaling takes place. As a result, immune cells have abnormal trafficking and function.

CXCR4 gain of function affects neutrophils, B cells, T cells, and dendritic cells, and this results in a broad spectrum of immunodeficiency and the characteristic neutrophil morphology of myelokathexis, which you can see here in this figure, where neutrophils have widely separated nuclear lobes connected by fine, long strands of chromatin. They often have vacuolization as well, as you can see here.

So strategic measures should be employed to identify the underrecognized diverse presentations of WHIM in order to provide prompt assessment and diagnosis. Importantly, don’t wait for all four features of WHIM to consider the diagnosis. Neutropenia and infections are the most common presenting features, but they are not universal, so it's important to Think Zebra as recommended by the Immune Deficiency Foundation. The younger the patient at diagnosis, the better. And it's important to test every newborn with a family history of WHIM, regardless of lab results or clinical condition.

The diagnostic approach is multipronged. The immunology approach includes measurement of lymphocyte subsets, immunoglobulin levels, and IgG responses to vaccines. The hematology approach includes multiple complete blood counts with differentials to measure absolute neutrophil counts and absolute lymphocyte counts. Peripheral blood smear and bone marrow examination may be used to look for myelokathexis, which is diagnostic of WHIM syndrome but easily missed and not always present. The genetic approach is the most specific.

Sequencing of the responsible gene, CXCR4, is diagnostic and should be employed for family members of known patients with WHIM syndrome. For patients with some of the features of WHIM syndrome, it may be more reasonable to use a next generation sequencing panel. CXCR4 is included in most NGS panels for neutropenia, inborn errors of immunity, or primary immune deficiency. These panels

are recommended when the diagnosis is not clear, as they are broader in scope, and they also allow detection of other inherited disorders with overlapping phenotypes, such as severe congenital neutropenia or some of the immunodeficiency syndromes with neutropenia. Please note that the invitae IEI panel is available without charge in a sponsored program for suspicion of WHIM listed here in this link. Consider whole exome or whole genome sequencing if CXCR4 is normal in a clinical picture highly suggestive of WHIM; this may turn out to be a WHIM-like syndrome with the clinical features, but not the genetic signature.

It's also important to consider WHIM syndrome when a newborn screen shows decreased numbers of TRECs. These T cell receptor excision circles are detected by PCR using DNA from dried blood spots from newborns. TREC levels are used as a biomarker for thymic output as TRECs emerge as a byproduct of T cell receptor V(D)J gene rearrangement during T-cell development. So finding of TRECs being decreased is sensitive for severe combined immune deficiency, SCID, but it's not specific. In a retrospective study of 6 infants with WHIM syndrome, 3 had had significantly decreased TRECs on newborn screens. So WHIM should be on the differential diagnosis of decreased TRECs with normal screening for SCID, and the decreased TRECs should not be dismissed as a false positive.

Thank you very much for your attention.

Announcer:
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