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You Don’t Know WHIM Syndrome (A Chronic Neutropenic Disorder)

Announcer:
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Dr. Newburger:
Hello. I'm Dr. Peter Newburger. And I'm Professor of Pediatrics and Molecular, Cell and Cancer Biology at UMass Chan Medical School. I'm also Attending in Hematology at Boston Children's Hospital. I'll be speaking today on the topic: You Don’t Know WHIM Syndrome (or Chronic Neutropenic Disorder).

WHIM is a serious disease with diverse presentations. The classic tetrad WHIM may not be present in all patients, and in fact, the prevalence of clinical findings in a large international cohort included neutropenia in 98%, lymphopenia in 88%, infections in 88%, but hypogammaglobulinemia in only 65%, and warts in 40%. This is probably a function of the ages of onset. Infections were present very early in life, neutropenia was first detected in early childhood, as was lymphopenia, hypogammaglobulinemia a bit later, and warts, which take some time to develop, were recognized at a mean age slightly over 12 years. I did not include myelokathexis in this grouping; only 23% of patients in the cohort presented with all features of the WHIM acronym, because myelokathexis was used only as a confirmatory, not a diagnostic feature.

WHIM is a serious disease that is associated with both morbidity and mortality. In the same series infections included pneumonia, otitis media, both the most common, as well as cellulitis, UTI, omphalitis, osteomyelitis, deep soft tissue abscesses, cellulitis, and sepsis/meningitis in 13%. The bacterial pathogens included, but were not limited to H. flu, strep pneumoniae, Klebsiella, Staph, and Proteus. Importantly, pathogens also included viruses, particularly human papilloma virus, and to a lesser extent, EBV. These patients had a vicious cycle of recurrent lung infections that led to bronchiectasis. And bronchiectasis, of course, led to more recurrent lung infections, leading this patient to have the CT scan image that you see here.

The sequelae of the infections included hearing loss due to the recurrent otitis media, pulmonary insufficiency due to recurrent pneumonias, and virus-related cancers, including EBV-associated lymphomas and HPV-positive genital and cancers. Patients also had chronic periodontal disease. The syndrome also includes autoimmune disease, which was seen in 21% of the cohort. These included cytopenias such as immune thrombocytopenia, autoimmune hemolytic anemia, and their combination in Evans syndrome, as well as type 1 diabetes, thyroiditis, vitiligo, arthritis, and hepatitis. Another feature of the syndrome, not immune related, is heart disease, the most classic being Tetralogy of Fallot, but also a variety of other congenital heart defects and Wolff-Parkinson-White syndrome.

The morbidity of WHIM goes beyond the specific disorders that I've described, and includes psychosocial morbidities, the result of hospitalizations, absences from school and work, resultant underemployment, and social stigma of a chronic disease. Mortality resulted from meningitis and sepsis from HPV-related carcinomas and from attempted cure by bone marrow transplant. Importantly, low mortality could be achieved with early proper treatment.

So early diagnosis and treatment is essential in this disorder in order to prevent irreversible end-organ damage, such as bronchiectasis and hearing loss, which is significantly more common in patients with late diagnosis versus early diagnosis. In the cited study, those who had a median age of diagnosis at 5 years, included 27% with bronchiectasis and three patients with hearing loss secondary to infections. However, in a cohort of patients with a family history of WHIM, so they had a median age at diagnosis of 1 year or less, only one patient had bronchiectasis and non-developed hearing loss.

So to sum up, this is a serious disease with important morbidity, some mortality, and I emphasize once again the importance of early diagnosis. Thank you for your attention.

Announcer:
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