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WHIM Syndrome Treatment: We Can Do Better!

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

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Dr. Walter:
Good morning. My name is Jolan Walter, and I am the Division Chief and Robert A. Good Endowed Chair of Pediatric Allergy and Immunology here at University of South Florida at Johns Hopkins All Children's Hospital. And today, I would like to share with you my concept on WHIM syndrome treatment, how we can do better.

My presentation will be in two sections. First, I will talk to you about a unique case study, and then we will draw some conclusions from this family history.

Looking at the family that I will share with you, our index patient, and this is a patient of Dr. Eyal Grunebaum from Canada. Is a 6-year-old male who came to his clinic with history of pneumococcal pneumonia and sepsis, recurrent ear infection, and amoxicillin prophylaxis. And as you can see on the right-hand side, the patient had normal lymphocyte panel and immunoglobulin levels were a bit on the lower side. So he did have hypogamma. He had no history of warts at that time. There was some history of infections and neutropenia. So he was sort of meeting the clinical criteria for WHIM syndrome.

And when the patient visited, as usual, we asked family history, and his 34-year-old father was questioned about his medical history. He did have upper and lower respiratory tract infections. Had a few warts on his finger, sinus infections, and other type of infections, and a low blood cell count. So compared to the little boy, who is 6 years old, the father had more severe hypogammaglobulinemia, and he already displayed the history of warts, recurring infections, and neutropenia. And because of the history of Dad's low immunoglobulin levels, there was an immediate response to it clinically to replace immunoglobulin. So this is not an uncommon treatment in WHIM syndrome. If patients have low immunoglobulins and infections, many patients would be receiving immunoglobulin therapy.

Moving further on, in the family, there was also a 42-year-old aunt, as you can see in the middle of my chart. This aunt was not as severely affected. She had warts, had a mild variant of hypogammaglobulinemia with few infections and neutropenia. And there were other members of the family in the third generation, including the grandfather and grandmother, who also had history of infections.

So obviously here in this case, there was a family with multiple affected members of the family and an inheritance that implied that it was an autosomal dominant disease, where Dad and son and even aunt shared similar clinical features.

And when we looked at a 19-year-old niece in the family, you can see that niece on the first generation of one 19-year-old in the middle of my chart, she again had no words, mild hypogamma, some infections and neutropenia. And these patients are much harder to decide how to treat. The milder infections sometimes don't warrant immediate interventions with prophylactic antibiotics or immunoglobulin replacement therapy. However, you have to keep in mind that their clinical presentation can escalate.

So quickly reviewing the phenotypic diversity in the family with recurrent infections, hypogammaglobulinemia, neutropenia, and

lymphopenia, most of them had some level of low IgG levels. They had infections, either severe or mild. And all of them had evidence of neutropenia. We sort of made them qualify for evaluation for WHIM syndrome. And the treatment actually ended up uniformly immunoglobulin replacement therapy, all patients required subcutaneous Ig at the time of diagnosis. And the indications in the father and the index case required it because of invasive infections, whereas in case of the aunt and the niece, the fact that they had low immunoglobulin levels with some infections was already qualifying for immunoglobulin replacement therapy. And during the evaluation process, the entire family was tested for WHIM syndrome, and they were found to have a pathogenic CXCR4 variant.

So that takes me to the whole idea of how to think of WHIM syndrome, and what is the treatment journey for a patient. On the left-hand side, I'm highlighting some of the common diagnostic features that can occur in younger children. They can have leukopenia, neutropenia, defective immune responses, possibly abnormal vaccine responses. And this can be alarming and may make the physician decide for treatment with immunoglobulins.

In the middle of the section, you can see the young adults and adults with more severe infections, EBV-associated lymphoproliferation, recurrent sinopulmonary infections such as otitis media, sinusitis, pharyngitis, cellulitis, infection of the skin, HPV, and warts, periodontal infections. And every infection would have its own treatment strategy, including antibiotics or antimicrobials, antiviral therapy, but overall, immunoglobulin replacement therapy could be a mainstay of the best treatment for these patients. I do want to emphasize that patients, because of their tendency for HPV warts, could benefit from immunizations with Gardasil. And there is a possibility that these immunizations will have the patient to prevent progression into genital herpes, HPV, and potentially have them not to have a risk for cancer development.

Which is taking me to the right side of the graph where the long-term and life-threatening complications are listed for WHIM syndrome. Some patients could develop lymphoma, and those patients with lymphoma would need aggressive chemotherapy. Besides the typical lymphoma, there is also evidence of squamous cell carcinoma, cervical dysplasia, and cancer related to HPV. So these are very important entities to monitor your patient for and treat them accordingly.

We also because, with the history of recurrent infections, patient can have chronic changes in their lung, including bronchiectasis and chronic obstructive pulmonary disease. We actually have shown in our paper that patients who were diagnosed at birth through family history could avoid this progression to bronchiectasis by having closer medical care, early treatment with antibiotics, and immunoglobulin replacement therapy. So there is a chance that by treating early these end-organ damages don't develop. That also includes hearing loss, which can happen in children secondary to their repeated ear infections, and again, could be avoided by proper immunoglobulin replacement therapy.

And lastly, what I would like to emphasize in the last part of my talk is that CXCR4 antagonists are on the rise. We have plerixafor available. It's an intravenous medication that doesn't have indication for WHIM syndrome, but it does act through the CXCR4 receptor. And among that line of intravenous and oral medications that are in clinical trials, there's a possibility that instead of treating and Band-Aiding a clinical problem, we could actually get to the root cause of the disease and influence the pathway that is overactive with CXCR4 antagonist.

So overall, there's a lot of excitement about how to treat WHIM syndrome. We have to use supportive therapy, and there is a potential in the future for targeted treatments.

Thank you so much for your attention.

Announcer:
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