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Managing Monogenic Autoinflammatory Disease: What Rheumatologists Need to Know

Announcer:
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Here's your host, Dr Jason Liebowitz.

Dr Liebowitz:
A monogenic autoinflammatory disease can cause many unexpected symptoms and side effects. But rheumatologists may have found a way to identify the genetic mutations leading to these symptoms. This is ReachMD, and I'm Dr Jason Liebowitz. Joining me to discuss what rheumatologists need to know about the genetic mutations leading to monogenic autoinflammatory diseases is Dr Bella Mehta. Dr Mehta is an assistant attending physician at the Hospital for Special Surgery and an assistant professor of medicine at the Weill Cornell Medical College in New York City. She specializes in research and care of patients with different rheumatic conditions, including Still's disease. Dr Mehta, thanks for being here today.

Dr Mehta:
Thank you so much, Dr Liebowitz, for this kind introduction, and I'm excited to be here because monogenic autoinflammatory diseases are often underrecognized and very important for a rheumatologist to recognize and start treating them early. So, let's talk about it a little more.

Dr Liebowitz:
Wonderful. So, to start with, Dr Mehta, can you tell us what defines a monogenic autoinflammatory disease? And what are the most common examples of this type of disease?

Dr Mehta:
So, monogenic autoinflammatory diseases are defined as something which has a single gene mutation that results in disorders characterized by episodic or persistent, seemingly unprovoked inflammation, without evidence of high titer autoantibodies or antigen-specific T lymphocytes. Basically, as the terminology goes, it's monogenic, so single gene, and how I think of it is that these are patients which do not manifest as typical autoimmune diseases.

These are thus autoinflammatory, and that's why they don't have autoantibodies or T lymphocytes.

The typical examples that we as adult rheumatologists see is FMF, or familial Mediterranean fever, and nowadays, much more recognized is the VEXAS syndrome. VEXAS syndrome was recently discovered, if you can say, at the NIH, and it's characterized by vacuoles, E1 enzymes, is X-linked, autoinflammatory, and somatic, and that's the nomenclature of VEXAS. Some of the other examples, which are much more common in the pediatric population, is the TRAPS syndrome, or the tumor necrosis factor receptor-associated periodic syndrome. The other one is CAPS which is cryopyrin-associated periodic syndrome. The others include Muckle-Wells syndrome, familial cold autoinflammatory syndrome. All of these are much more common in the pediatric population. As a rheumatologist, as an adult rheumatologist specifically, again, as I said, we see FMF and VEXAS.

Dr Liebowitz:

Wonderful. And given that monogenic autoinflammatory diseases typically present in childhood, when should a rheumatologist look for these diseases in their adult patients?

Dr Mehta:
So, some of the typical features of autoinflammatory diseases, such as FMF, familial Mediterranean fever, include recurrent fever, abdominal pain, chest pain, joint pain, rashes. Again, fever and serositis are pretty common in FMF. Initial attack occurs usually before the ages of 10 or 20 years, but also much more common in the later decades. So, there can be patients that can be manifesting FMF syndrome for the first time when they are older than 50. It is much more predisposed in certain genetic ancestries, and it's important to evaluate for bouts of fever followed by symptom-free periods. That way, we know that this is not an infection, but an autoinflammatory cause of the fevers. In some cases, in severe FMF, there could be continuous acute phase response, but most patients will have bouts of fever which go away without antibiotics or something.

Again, and whenever you are diagnosing autoinflammatory diseases, it's also important to make sure that we've done the testing for, or talked about, infections and malignancies because sometimes those are the differential diagnosis for these patients. Patients who have relapsing polychondritis may also present with symptoms related to the cartilage, maybe inflammation in the ear, you know, changes in the voice, things that are not typically present in autoimmune diseases. And it's important to connect clinical features which can unify the diagnosis, such as presence of pyoderma gangrenosum with arthritis, or pustular psoriasis with osteitis, which, again, much more common, these sort of symptoms in the pediatric population. I think detailed family history and ethnicity of the patient may provide some clues into possible monogenic autoinflammatory diseases, because they are often hereditary.

Dr Liebowitz:
Thank you, that's a very helpful summary. So, Dr Mehta, looking to the future, what challenges can we expect to see when it comes to the management of these diseases?

Dr Mehta:
I think there's a huge need to recognize these diseases early and referring these patients early on to rheumatologists and the correct specialists. Sometimes patients go on undiagnosed for many, many years, suffering through the consequences of diseases. For example, there are FMF patients who have had this for years and by the time they're actually seen and referred to the proper specialist, they already have developed amyloidosis or something like that. So thus, early referrals. We as a rheumatology audience also need to recognize these small signs and symptoms early.

Next is understanding the clinical significance of loop antigens variance because there are patients who may not typically present in the textbook picture. So, we need to recognize that and look into it in a little more detail. Also, given that these are rare diseases,there is less long-term safety data or efficacy data, and I think as a community we need to work on it and start collecting the data systematically.

We also need to understand the genetics and the pathophysiology of these different diseases in much more detail. There are a lot of patients who are underdiagnosed because currently, the symptoms do not exactly fall into 1 category of diseases that are recognized right now. But there are a lot of monogenic diseases which will be recognized going forward in the future, as we have much more genetic testing and much more cohorts that we build. So, even though these diseases are unclassified right now, we need to understand that in the future we'll understand these genetics and be able to treat them much more in a precision medicine way.

So, I think overall there's a lot of challenges, but there's a lot of hope in the future because we are all getting towards recognizing these. And I think the VEXAS syndrome is a true example of that, that it was recently coined and diagnosed. There have been patients who have been suffering with this for years but now that we've recognized it, it's much, much more easier to treat them.

Dr Liebowitz:
Excellent. That's an extremely helpful summary, and a great way to round out our discussion on this topic. I want to thank my guest for helping us better understand monogenic autoinflammatory diseases. Dr Mehta, it was a great pleasure speaking with you today.

Dr Mehta:
Thank you so much for inviting me, and I think, again, knowing more about these diseases will help us as a community diagnose this much better.

Announcer:
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