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The Evolving Science of Chronic Spontaneous Urticaria

Announcer:
You're listening to *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. Here's your host, Dr. Gates Colbert.

Dr. Colbert:
Welcome to *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. I'm Dr. Gates Colbert, and joining me to discuss how advances in autoimmunity and endotyping are shaping our understanding of chronic spontaneous urticaria, or CSU for short, is Dr. Gordon Sussman. He's a Professor of Medicine at the University of Toronto and a staff physician in the Division of Immunology and Allergy at St. Michael's Hospital. Dr. Sussman, it's great to have you with us today.

Dr. Sussman:
Thank you. It's a pleasure being here, and it's very good to talk about chronic urticaria anytime.

Dr. Colbert:
So let's start by doing some level setting, Dr. Sussman. How has our understanding of CSU's underlying pathogenesis evolved in recent years?

Dr. Sussman:
So I'm going to start by saying, I still don't believe the concept of chronic urticaria is well understood. It's a disease. It's an autoimmune disease. We know what it is, but it's very disabling. It's a condition that has many mental consequences: anxiety, depression, and even suicides.

It's something that physicians have to really understand and comprehend to understand the pathogenesis. If we look at the Urticaria Voices, which is a recent survey on chronic spontaneous urticaria, which is CSU, we see that people are still treating with prednisone and with first-generation antihistamines—medications that we try not to treat with.

Also, there's a disconnect between how physicians view how patients are doing and how patients are actually doing. If you ask a physician, 70 percent say the patient is doing well. But if you ask the patient, 80 percent say they're not doing all that well. We're not there when they're scratching and itching and they have these stupid wheals and swelling.

So that's important to understand. With that, we know today that chronic urticaria is autoimmune. It's not a food allergy. It's not an allergy that we can't figure out. And it's a fairly complex heterogeneous disease.

Dr. Colbert:
Now, a key development has been the recognition of autoimmunity's role in its pathogenesis. So can you walk us through the different endotypes that have been identified and what distinguishes them?

Dr. Sussman:
For sure. It's my pleasure. So over the last several years, there's been the understanding that chronic urticaria is autoimmune. And then there's been two basic types that have been identified. One type is the type I, which is anti-IgE against self. If you look at patients, often they have thyroid autoimmunity and they have IgE that can be directed against self. There's over 250 self-allergens that have been identified. And if you look at the IgE repertoire of patients, a great percentage of our CSU patients is directed against the self. It's directed against their self. And that's thought to be a pathogenic factor in looking at this type of chronic urticaria.

The second type is autoimmune urticaria, which is IgG-directed against IgE or the Fc receptors on mast cells. This type of chronic

urticaria is difficult to treat. It's associated with an autoantibody—an IgG autoantibody—to the mast cell receptor. It's not on everyone, but it's on a significant percentage of patients.

And it's associated with various biomarkers that have been identified, and we'll discuss that as we go along.

Also, there are people that have both types. They start out, it seems, with the autoimmune, but they also have the autoallergy. So we're looking at overlapping pathogenic mechanisms in this subset of CSU patients.

Dr. Colbert:
As a follow-up to that, how do these endotypes translate clinically? For instance, are there any differences in disease presentation, severity, or progression that we should be aware of?

Dr. Sussman:
Yes, chronic urticaria is pretty heterogeneous. If you look clinically, factors that will predict more severe disease is duration—how long it's been there for—the presence of angioedema or swelling, and also the association with chronic inducible urticaria, which is called CINdu. Those people have a more severe disease.

If you look at endotypes, type I is easier to treat than type II autoimmune type. So the autoallergy type is generally easier to treat than the autoimmune variant of chronic spontaneous urticaria. We identify the type II through several ways. One is by doing a skin test with their own serum. That's called the autologous serum skin test. But also, we can look at the presence of the autoantibody to the mast cell receptor and the presence of basopenia, as well as eosinopenia and the low IgE. The low IgE can be a biomarker that's being looked at in people that have more severe, or the type II, autoimmune disease.

The other biomarker is basophil activation, which is either histamine release or just an activation test, which is also associated with the type II, or the autoimmune variant of CSU.

Dr. Colbert:
For those just joining us, this is *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. I'm Dr. Gates Colbert, and I'm speaking with Dr. Gordon Sussman about our evolving understanding of CSU's pathogenesis, including the role of autoimmunity and endotypes.

So, if we continue examining how this condition appears in clinical practice, about 10 percent of patients with CSU present with angioedema alone. With that in mind, Dr. Sussman, how can we distinguish these cases from other forms of angioedema?

Dr. Sussman:
If you look at chronic urticaria, it's swellings, and extreme swelling is called angioedema, where your lip is swollen, your hands are swollen, or your feet are swollen. And that is pretty disabling. And it's something that we have to recognize as part of chronic spontaneous urticaria.

If you look at the other end, where there's wheals and not the swellings, that is associated with autoimmune or autoinflammatory disease. Usually, they have fever syndrome, they may have fatigue and joint pains. And it's treated differently. So it's very important to recognize these variants because the treatment is different.

Autoimmune urticaria is treated with a number of new medications, including an anti-IgE and a BTK antagonist, and different ways to treat chronic urticaria, including anti-IL-4/13. If someone has angioedema, it would be nice to have a biomarker to be able to identify the group that has angioedema, which is mast cell mediated. This is much more common than the rare type, which is angioedema associated with bradykinin, which can be associated with life-threatening laryngeal edema.

The way we recognize that is by doing a complement profile, which is a C4 and C3 antigenic and functional C1 esterase, but it's treated completely differently. HAE, we understand to the molecule. CSU, we don't. CSU, we're not there with biomarkers yet. And it's very important to be able to identify that group of people so we can treat specifically for the type of angioedema that they have.

Suffice to say, however, that we have to identify at least the people that have bradykinin-induced swelling, because it's a completely different treatment.

Dr. Colbert:
Looking ahead before we close, Dr. Sussman, how might endotyping and biomarkers help move us toward more personalized treatment approaches for CSU?

Dr. Sussman:
That's the most important factor—that we can treat with different drugs, right? So it should be fun to treat chronic urticariam because

there's so many new treatments that are down the pipeline. For instance, the anti-IgE, which was first licensed—in Canada, at least—in 2015, was a game-changing treatment for chronic urticaria. It's not intuitively obvious that an anti-IgE would be useful, because chronic urticaria, like I said, is not an allergy. And that's probably because of the type I, where the anti-IgE will decrease the signal for mast cell degranulation.

There's also treatments that decrease the activation of mast cells. The BTK antagonists, which are available in the US—not yet in other countries in the world—will decrease the activation by BTK and the autoantibody production. The KIT mutation antibodies are a very exciting treatment that deplete mast cells and may be associated with long-term remission.

And the anti-T2 antibodies, like the anti-IL-4/13, can also be associated with longer-term remissions when they stop. So these disease-modifying treatments are very exciting in this field of chronic urticaria. So this all leads to these new and exciting treatments that we're trying to tailor for individual patients.

Dr. Colbert:
Those are great comments for us to think on as we come to the end of today's program. And I want to thank my guest, Dr. Gordon Sussman, for joining me to share his insights on the role of autoimmunity and endotypes in chronic spontaneous urticaria. Dr. Sussman, it was great having you on the program.

Dr. Sussman:
Thank you very much. It's my pleasure being here, and thank you for having me.

Announcer:
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