

TRANSCRIPT

episode #1: Unravelling the mysteries of the tick induced alpha-gal allergy

Zac Stritch-Hoddle Host

00:00

Ladies and gentlemen, welcome to Tick Tick, Boom!. I'm your host, Zac Stritch-Hoddle, and today we're diving into the strange and relatively uncharted world of Alpha-gal allergy. Let me set the scene. Nestled in the beautiful landscapes of Sydney's northern beaches, with its gorgeous coastline and easy going lifestyle, life seems perfect. However, in the early 2000s, a strange phenomenon started to unfold. People began experiencing bizarre allergic reactions long after they had eaten anything and without any previous history of allergic reactions. In the middle of the night, an alarming wave of hives swelling and a sudden struggle for breath would grip them, leaving victims in a life-threatening predicament. This is no ordinary allergy and it left everyone puzzled. Now this is where I'd like to introduce you to Professor Sheryl van Nunen, the doctor who finally solved the mystery of the allergy in the night time.

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In an unexpected turn of events, these reactions were discovered to have started because of a tick bite. Professor Sheryl van Nunen is a clinical Professor at both the University of Sydney and Macquarie University, a consultant physician in allergic diseases and a visiting medical officer at Northern Beaches Hospital, as well as a convener of Tiara [Tick Induced Allergies Research and Awareness]. Professor van Nunen was head of the Department of Allergy at Royal North Shore Hospital for more than 26 years. She is a clinician and medical educator who, in 2007, first described the association between mammalian meat anaphylaxis and prior tick bites. She has more than 175 publications to her credit. Thank you for joining me today. Professor van Nunen, could you walk me through how you first discovered this connection between two things that initially seemed completely unrelated: people having a tick bite and then later developing this delayed allergic reaction to mammalian meat and other mammalian animal products?

Professor Sheryl van Nunen Interviewee

02:05

Well Zac it started about 30 years ago. Well, 25 years ago 1987, I saw the first person with this complaint, but it started becoming quite a common problem from about the late 90s, early 2000s. I was working in an area where I saw almost everybody who'd had an anaphylaxis, and that's unusual, and I had worked there for about 20 years beforehand, so I knew that this was novel. Now, as an immunologist, you have a background of working with the immune system, looking at parasites. Parasites provoke IgE. IgE is involved in parasite defence and therefore you could see there would be a possible connection between a parasite such as a tick and the production of IgE. And so it seemed that when people were coming in and telling me they had had an anaphylaxis in the middle of the night, and when I asked them in the way that I do, about all the other possibilities for allergy, like asthma, rhinitis, eczema, food allergy and insect allergy that they'd say well, I don't have an allergy to an insect, or in fact a few of

them did. They had large local reactions to tick bites. They say I've been bitten by ticks doctor. So after you've seen a few people like that, you sort of think well, ticks are parasites.

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These people have an allergy and so you get them in and you painstakingly. They bring in everything they ate the night before. You're desperate because there's no other allergy. That takes about three to six hours to get going. So the only thing you can think of is to say bring all your food in, we'll check you. You can find these small results with food. When you prick the food and prick the person, you say, well, I'd like you to avoid meat. And then they do, except somebody shafts them, gives them meat by accident and they have another reaction. And then when they avoid it again.

03:57

They don't react. So there you've got mammalian meat allergy a middle of the night, anaphylaxis and people who've had tick bites.

Zac Stritch-Hoddle Host

04:04

When did the medical community determine that this was a more global phenomenon, as opposed to just a few isolated cases?

Professor Sheryl van Nunen Interviewee

04:12

It's actually been very quick, Zac, because this allergy, from the point of view of being available for people to see in the medical literature, is only 16 years old. So there's been a phenomenal amount of work done around the world. So we made the association in 2007, and 16 years later there's been an enormous amount of work done. So two clinical observations started this all off. One was noting that tick bites and meat allergy were associated, which was the Australian report. And then the other one was an Oncologist working in the US chap called Dr Bert O'Neal and there'd just been a magic bullet called Cetuximab introduced. It's wonderful for colon cancer and hidden neck cancer and he was treating people in the South East and United States and he noted that there was a really high chance of having a near-fatal or a very serious allergic reaction when this drug was given intravenously and he thought that's very odd. So in the US, Platts Mills and his group started looking at this Cetuximab and they found the particular part of the molecule, the alpha-gal, that part of the meat which is the actual allergen within the meat and that's been added to around the world. This took off a little bit like a grass fire really, and then we had the French showing that exercise and alcohol make it worse.

05:45

On the individual episode we had the people in Sweden, Marianne Van Haag and her group. They sliced the tick up. We thought initially that the tick had bitten a mammal and transferred it in its saliva. But in actual fact that tick's making alpha-gal and it does that to protect itself against the infection and because the tick in Australia's had to find a new host, largely because we started getting rid of the foxes, baiting the foxes. So then the tick we think is making more alpha-gal. It's in its saliva and in its mid-gut, as our Swedish colleagues have shown, and it's charged with this. It wouldn't have done that before because it's quite used to the foxes microbiome, but now it has to defend itself against the new bugs on the new host.

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So more ticks have more Alpha-gal and when they inject the person they actually inject. Our tick doesn't have any cement, so our tick has quite a deep feeding tube, a long feeding tube, and that means that the tick's

injecting the alpha-gal below the level in the skin where the meat and greets cells of the immune system are, and therefore the human host, the accidental human host, is now forced to make an immunological reaction to that and after two tick bites, around 50% of people will make allergy antibody to it and not other, well the other antibodies as well, but not just the other antibodies. And then when they have meat three to six hours later because that's the time it takes for the digestion to release the allergen they have an immediate, rapidly evolving anaphylaxis. When it's injected back into the vein, the inferior vena cava, the largest vein in our body.

Zac Stritch-Hoddle Host

07:40

So do we actually know how many people are affected by this allergy?

Professor Sheryl van Nunen Interviewee

07:45

The actual prevalence is not exactly known in a lot of places. The German researchers have looked at that and they went to a tick hyperendemic area in the forest in Germany, Baden-Württemberg, and they showed that about 35% of people where ticks are really what we call hyperendemic or easy to get hold of that, in those 35%, only about a little over 8% of people would be manifesting mammalian meat allergy symptoms. So one of the problems with this is that you could have around 30% of people positive to the Alpha-gal specific IgE, but only around a third of those people will know that. And then this is the problem when you consider the other findings that we've managed to establish, such as the increased burden of coronary artery disease. So this means it's incredibly important for people to, just as we used to slip, slop and slap and not do coconut oil 40 years ago, then it's equally important, if you live in a tick endemic area, to not have a tick bite, if you can manage it, because the reason people have mammalian meat allergy or tick anaphylaxis, which is a separate allergy to a protein in the tick saliva, is that that tick has injected Alpha-gal. Alpha-gal into them and has made them sensitised to Alpha-gal, which means they could react if they had Cetuximab, never having had reaction to meat or never having had an anaphylaxis to a tick. So Alpha-gal coats the tick salivary protein. So we've had an epidemic of tick anaphylaxis as well, and that's due to the function of Alpha-gal as a sugar coating the protein in the tick saliva and making that more likely to be recognized by the immune system as well.

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So if ticks cause it, then the one thing we should be doing is not having a tick bite, and prevention is the best approach. So we'd like people who live in tick endemic areas to treat their backyard, if they can ask the pest controller in. We like them to dress for the occasion. Dressing for the occasion involves a long sleeve t-shirt with a crew neck with a long tail tucked into your long trousers, tucked into your socks, and all treated with the tick knockdown agent, permethrin, if you can, and then the Deet repellent or Picaridine applied to the interface between your skin and where your clothing starts, and that will give you up to 99% protection from tick bites.

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You get another chance, though, because if you are bitten by a tick, then what we'd like you to do is to kill the tick where it is. So don't scratch anything you can't see, because it could be a tick. Don't disturb a tick because she'll squirt allergen into you as she's trying to get away and freeze the tick where it is, so it can't squirt and then let that tick detach spontaneous feet, drop off by itself, because that's the best way of doing it. About one centimetre above the tick you apply this, give it five sprays, because that's what we did in the research, and then wait five minutes, have your magnifying glass out, see if you can see the tick's dead and then wait for it to drop off. If it's not dropping off within a certain time or it's still moving, then give it another five sprays and, yes, you may get a freezer burn, but that's probably better than living your life with alpha-gal sensitisation or mammalian meat allergy.

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11:31

So for everyone listening, always remember if you're bitten by a tick, freeze it, don't squeeze it.

Professor Sheryl van Nunen Interviewee

11:37

Perfect.

Zac Stritch-Hoddle Host

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And when should someone use permethrin cream?

Professor Sheryl van Nunen Interviewee

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With the children who are under four. The manufacturers of the freezing sprays would rather those were not used in children, and there are situations in people who are over four, for example, if it's near your eyes or near your genitals where you can't use the freezing spray and so the permethrin cream, you can squeeze up a blob on the top of the tube and then touch that to the tick without squashing the tick or disturbing the tick at all, and then the tick will die. And again you leave that a certain amount of time and then scrape it off. We say credit card, something like that edge of the knife.

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12:18

Do all types of ticks trigger this response?

Professor Sheryl van Nunen Interviewee

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As the entomologist Stephen Doggart will tell you, that in Australia, about 97% of people are bitten by the Australian paralysis tick, the common name, which is *Ixodes holocyclus*. We have established in our research that there's a second tick in Western Australia, in the southwest of Western Australia, which will transfer this around the world. That's been one of the other parts of this and it's been found a different tick in Central America, different ticks in Japan, different ticks in Europe, different ticks in Africa, different tick in America. So in all, there are probably about 16 different types of ticks around the world, so you can have a tick bite on any continent except Antarctica. I think that what's actually happening is that on any continent, we should not have a tick bite, because any of those ticks can actually transmit alpha-gal and mammalian meat allergy can result.

13:24

Some ticks are better at it than others. Our Australian ticks absolutely tops with causing this. Even when you review the recent estimates by the workers in the US in the CDC report Morbidity Mortality Weekly report a few months ago, they're only just approaching our 2018 prevalence figures and I see three or four people a day with this, two days a week. So I think that our Australian tick is very good at it. The American tick is very good at it. The European tick will do it, but it's not as common for people to have it when they're bitten by that tick as it is. Tick anaphylaxis is quite uncommon around the world, but Australia, I think, probably close to a little over 500 people with tick anaphylaxis I've seen, whereas the rest of the world is one Californian, one Frenchman, six Spanish Goatherders, 12 Japanese people, and they're now 500 plus. So now I'm not the only person who sees people with tick anaphylaxis. So this is the second epidemic following the mammalian meat allergy anaphylaxis epidemic.

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14:41

What would you say to someone who has just been newly diagnosed with these allergies?

Professor Sheryl van Nunen Interviewee

14:46

With the mammalian meat allergy anaphylaxis and with the tick anaphylaxis they're both preventable if you don't get a tick bite. It can't happen. Now, intriguingly, with the tick anaphylaxis only the adult tick will give rise to an anaphylaxis to the tick's salivary proteins. With the mammalian meat allergy anaphylaxis, however, that doesn't happen when bitten by by a tick. It happens because you've been bitten by a tick and it takes about two weeks for the antibody to sufficiently often that happens.

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You can be sensitised from a bite from any blood-sucking life stage of tick larval, nymph or adult.

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So people with mammalian meat allergy have a number of tick forms that can sensitise or recharge their allergy, whereas not as many people have a tick bite from adult ticks as have from nymphs.

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So the tick anaphylaxis people have a better chance of avoiding. And if they don't touch that tick and it's treated as we said, freeze it, kill it in situ and then have it removed without any disturbance of the tick or let it detach spontaneously they don't have an allergic reaction. So we think that if you deal with the tick properly, you're reducing the chance of recharging or developing mammalian meat allergy or anaphylaxis to mammalian meat. So it's all about avoiding the tick and, more importantly, what we've shown recently. So with the tick anaphylaxis, if you've got that, you've got that for decades, like bee venom allergy, jump around allergy, any of the other insect allergies. But if you've got the mammalian meat allergy, then what we see is within 12 to 18 months there's a rapid reduction in the amount of allergy antibody you have directed against the alpha cow and within three to four years that's low enough for quite a few people the majority to be able to eat meat again. So not only is it preventable, we see it as being curable.

Zac Stritch-Hoddle Host

17:07

How will someone know if they actually have this allergy?

Professor Sheryl van Nunen Interviewee

17:11

Well, when it's an anaphylaxis, there's nothing else like it. There's nothing else once you've excluded semen allergy and latex allergy. That's a middle of the night. Drop down, drag them out. Anaphylaxis the diagnosis is mammalian meat allergy after tick bite until proven otherwise. So that's easy.

17:30

There are also people who develop urticaria or welts angioedema in the middle of the night and with that many people come to you saying I suspect that I've got the meat allergy now because there's been a fair bit of publicity about it and they know that there's a gap. And then we're seeing a lot of people now that have gut based mammalian meat allergy, where it's faster in onset because it's a local reaction in the gut. So within an hour to two hours people have eaten the meat and then they have absolutely agonising abdominal cramping, compared unfavourably to that of childbirth by women who've been there and done that. And then there's diarrhoea, not usually vomiting, but can occur in some. And then there's another part of the spectrum where they empty out both ends.

18:24

This is rare, it's about one in a hundred people do this and it's what we call food carbohydrate induced endocarditis syndrome, which is terrible cramps, both ends empty out, your blood pressure falls to your boots, your pale, your lethargic, you look as though you're going to die. We give you some fluid, intravenously, and it's all over within a couple of hours. So that is not an allergy, that's not Ig-mediated, but it's rare. So the majority of people will come in having had a middle of the night anaphylaxis or middle of the night allergy symptoms. Typical for allergy redness, itch, swelling. The three typical findings of IgE the E for red blood red, and so that's fairly typical, and then the gut-based ones, as we've discussed, very, very common.

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19:20

If someone is having an allergic reaction, what should they be doing?

Professor Sheryl van Nunen Interviewee

19:25

Take them off, treat them, take them off to the ED and Northern Beaches Hospital ED, where we live, it's very familiar with this problem. We do a lot of work, we work together and what we've got then is they know about it and then they send them on to us the immunologist analogous to do the testing. So at the moment we're testing for Alpha-gal specific Ig towards Alpha-gal to make that diagnosis, and our South African colleagues have done some work on this, bearing in mind the international effort. That's been amazing in the 16 years and they've looked at it and they will give us a figure of 5.5, means you're more than 95% likely to react to meat every single time you have it.

20:16

And if it's 2.0, whereas normally it's 0.10 or less, that's a negative. Then if it's 2.0, people will react on a number of occasions. That's harder to put together than an every time reactor and this allergy is also known for being an any time but not an every time reaction, which also makes it harder to put together. But once you've got that test done, then you've got confirmation. So it's always the clinical side or the history that the person's told you and the confirmatory test. You don't go with the test result by itself. It's got to be confirmed by the patient's story.

Zac Stritch-Hoddle Host

21:04

Do people always have the same kind of allergic response?

Professor Sheryl van Nunen Interviewee

21:08

No, they don't. So when you have a food allergy, there are a group of factors called amplifying factors, or the Europeans would refer to them as cofactors, and these apply to all food allergies. It's not just the meat. So if you wanted to have the biggest reaction you could, with whatever level of sensitisation or whatever allergy antibody level you had to the alpha-gal, you would really eat a lot of the meat. We could go to the local bus stop and 11 out of 10 people would say oh yes, if you eat more of your allergen then you'll have a bigger reaction. But the others people don't really know about. And those others are sleep deprivation, exercise, alcohol with the meal, having had a non-steroidal anti-inflammatory drug, like Nurofen or Voltaren or Aspirin within 24 hours before hand putting spice on it. Chili and capsicum contain capsaicin, which is a histamine releasing agent, which is why the police use it to irritate people, so that if they're doing bad things they stop. And then you've got some women, only reactive they're in their premenstrual phase. So any one of these are independent operators.

22:32

So we have people who will have a few hives if they have a small amount of meat or none, but if they have a roast lamb with a slow cooking and reheating it will bring out the allergen from the connective tissue of the animal where it is. So you've got this broken down, so you've got a big glob of the allergen in this meal. So somebody could have a lamb cutlet and not react. But if they have that slow roasted lamb, a little bit of chilli with it, have done their run before they come in for their evening meal, have a lovely glass of wine it's a Friday or Saturday night, they can relax.

23:16

And who doesn't like roast lamb? Who likes meat? So they have a larger amount of the meat and they have the anaphylaxis then and so they can be perplexed. Why can I have a lamb cutlet or why can I get away with bacon or prosciutto when I've had this anaphylaxis? So initially patients would be really and the idea of the parasite being involved with association with a food allergy my colleagues as well was sort of really? But then you see this entire spectrum and that's all to do with how the amplifying factors are acting in that individual.

Zac Stritch-Hoddle Host

24:05

Where should someone go if they want to get more information about this allergy? On behalf of Tiara, I'd like to extend our thanks to Professor van Nunen for a fantastic and really insightful conversation. A reminder if you've ever been bitten by a tick, always remember to freeze, don't squeeze. For more information on preventing Alpha-gal allergy, please visit TiARA.org.au, where you'll find research papers as well as show notes. Stay tuned for our next episode, where I travel to the Garvan Institute to speak with world-leading researchers on Alpha-gal allergy and Alpha-gal antibodies. Thanks for tuning in to Tick, tick, boom!