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# Tryptase Testing in Chronic Mast Cell Disorders and Acute Settings

ANNOUNCER INTRO:
Welcome to CME on ReachMD. This activity is presented by Dr. Phil Lieberman, Clinical Professor of Pediatrics and Internal Medicine in the Allergy/Immunology Division of the University of Tennessee College of Medicine, and is brought to you by the Academy for Continued Healthcare Learning and supported by an educational grant from Phadia US Inc. a part of Thermo Fisher Scientific. Before starting this activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

DR. CAUDLE:
Based on estimated prevalence of 6%, approximately 20 million people in the United States have elevated levels of serum tryptase. I'm your host, Dr. Jennifer Caudle, and I'd like to welcome Dr. Phil Lieberman to the program, who's joining me to share his insights on serum tryptase testing in clinical practice, and its importance in assessing mast cell disorders and anaphylaxis. Dr. Lieberman, welcome to the program.

DR. LIEBERMAN:
Good morning Dr. Caudle, and thank you very much. It is indeed a pleasure to be here.

DR. CAUDLE:
So Dr. Lieberman, can you tell us about the clinical importance of serum tryptase and its association with mast cells and mast cell disorders?

DR. LIEBERMAN:
The topic that we're going to discuss this morning, probably more than any other single topic in our field, allergy and immunology, has undergone the most explosive, expansion of knowledge in the last decade. So, it's getting more and more important for us to understand the use of tryptase. And we know, at this point in time, that it's clearly underemployed. So education about its use is crucial. And it's very important to our patients.

Tryptase represents as a molecule, the singest largest content of the mast cell granule and it is the best and most reliable biomarker for mass cell activation. Because of a new disease called alpha hypertryptasemia our knowledge about tryptase, as I noted has exploded. And we need to understand the fundamentals of the application of tryptase in the practice of medicine. This new disease alpha hypertryptasemia has boggled the imagination, because it has been manifested by a plethora of symptoms that could not be explained by any known pathophysiology until probably perhaps six months ago. And now for the first time we have, better knowledge about what underlies this disease, and that knowledge is applied throughout our field.

As we mentioned tryptase is the best and most reliable biomarker for mast cell activation. It is a diagnostic marker for anaphylaxis, for certain episodes of acute urticaria, and for this recently described hyper alpha tryptasemia. So we are using serum tryptase in many ways now. Any person who has ever experienced an anaphylactic reaction or an allergic reaction even non-anaphylactic to an insect sting, any person who has ever had anaphylaxis of unknown cause any person who presents to an emergency room or clinic with symptoms of anaphylaxis, or even with symptoms of acute urticaria any person who has a condition that suggests hyper alpha

tryptasemia, all of these would demand the measurement of a serum tryptase. The value of serum tryptase directly correlates with the severity of a reaction, it directly correlates with the risk of a reaction and the baseline level, normal level, of serum tryptase is 11.4 as a maximum and anything above that is abnormal. And the abnormality is characterized based on the clinical presentation of the patient.

DR. CAUDLE:
So, Dr. Lieberman, let's focus on mastocytosis for a few minutes. What characterizes this disease? And is it the same as mast cell activation syndrome?

DR. LIEBERMAN:
Great question. No, it is not the same as mast cell activation syndrome. Mastocytosis as a diagnosis requires certain characteristics to be documented, and in almost every instance, that requires a bone marrow. And in mastocytosis, the World Health Organization criteria for diagnosis is quite clear and explicit. Whereas in mast cell activation syndrome you do get release of mast cell mediators, and that it holds in common with mastocytosis. But you don't have the criteria for the diagnosis of mastocytosis on a biopsy. With mastocytosis, there is a proliferation of abnormal mast cells and they accumulate in many organs, the main one being the bone marrow. There is a great heterogeneity of presentation in severity.

The major symptoms of both disorders, of mastocytosis and mast cell activating syndrome are the skin manifestations, and urticaria and flushing are quite common. But, you can also get more threatening symptoms of anaphylactic shock and these are more common in mastocytosis than in mast cell activating syndrome. There isa way that you can screen for mastocytosis versus mast cell activating syndrome without a bone marrow, and that's by doing a mutational analysis of816V, which is the mast cell KIT receptor. And that is about 95% accuracy if the right test is performed. But for a full diagnosis, a bone marrow is indicated.

One more point is that mast cell activating syndrome also has strict criteria to make a diagnosis. They're distinct from mastocytosis, but they consist of the following three things. You have to have clinical evidence of mast cell mediated release, so things like hives and wheezing and shock, you have to respond to anti-mediator therapy drugs such as antihistamines. Perhaps most important, you have to have objective confirmation with elevation of mast cell mediators in the serum. And that requires, a serum tryptase.

DR. CAUDLE:
So what role does serum tryptase testing play in the diagnosis of mastocytosis?

DR. LIEBERMAN:
A serum tryptase in mastocytosis as in all the diseases characterized by mast cell activation must be performed. It is the least expensive, the most accurate, the most reliable, and the easiest confirmation of mass cell release, that we have. It would be elevated above 11.4. This is very important it would be a baseline determination. It can be obtained while the patient is asymptomatic, and it would be above 11.4 nanograms to indicate a diagnosis of mastocytosis.

DR. CAUDLE:
For those of you who are just joining us, this is ReachMD, and I'm your host Dr. Jennifer Caudle. Joining me to talk about serum tryptase testing in chronic mast cell disorders and acute settings is Dr. Phil LIEBERMAN.

So Dr. Lieberman, you shared with us some of the considerations related to serum tryptase testing in chronic mast cell disorders, such as mastocytosis. So let's move onto the acute setting of anaphylaxis. What's the role of serum tryptase testing in idiopathic anaphylaxis?

DR. LIEBERMAN:
Again tryptase is absolutely necessary because one needs to be sure of the diagnosis of idiopathic anaphylaxis. And, a serum tryptase in idiopathic anaphylaxis should be done at baseline when the patient is asymptomatic. Because if it's elevated, then that points you in the direction of mastocytosis, or hyper alpha tryptasemia. If you get an elevated serum tryptase at baseline, then it requires additional workup. You have to work up those two disorders. But perhaps even more importantly you should always get a serum tryptase if a patient presents with signs and symptoms of anaphylaxis, and that is crucial. Serum tryptase increases during the first 90 minutes after the onset of symptoms. And then it shows a steady decline in keeping with its half-life. So ideally, any patient presenting to you with the signs and symptoms of anaphylaxis should have a serum tryptase done immediately upon presentation. An important change in serum tryptase from baseline would be 20% above the baseline plus 2. So if a patient came inwith 10, it would be 2 for 20% plus 2 nanograms, or 14. These results can be crucial, especially for the allergist who may see this patient, in retrospect.

DR. CAUDLE:
Now, when you suspect a patient has idiopathic anaphylaxis, what do you think about when considering differential diagnoses?

DR. LIEBERMAN:

First of all you want to think about making sure you've got the right diagnosis. That's extremely important. And much like asthma, many patients who are thought to have severe asthma, have other conditions. So establishing the diagnosis as best we can, is important and that again, it's why a serum tryptase is so important.

The second thing you think about is what the cause is. And obviously  this too is extremely important because if you can find the cause, it's no longer idiopathic. And if you find the cause, oftentimes you can remove the cause, and therefore “cure the condition.” Everyone is familiar with common causes: food insect venom,  and drugs. The other differential diagnoses consists of other organ systems outside of anaphylactic events. For example, we occasionally see people with vasovagal reactions that are thought to be anaphylaxis, but they're cardiovascular in nature. An arrhythmia, for example, a sudden onset with loss of consciousness.

And then one very interesting syndrome, which is really important where I live in the southern part of the United States is the alpha-gal syndrome. Alpha-gal is relatively new as a discovery. And it is allergy to mammalian meat. But the key is, it's really not the meat that the patient is allergic to. It’s actually galactose-1, 3 alpha-galactose, which is a sugar. And the revolutionary finding that you can anaphylax to a sugar was very important. We know now that this condition is not only present in the south, where the vector is the Lone Star tick, but we have had, reactions in New York State, in Connecticut, in Massachusetts, in almost every state in the Union, because what we have learned is that other species of tick also can carry alpha-gal.  And the incidence of alpha-gal is growing tremendously. In our series of patients, it accounted for 30% of anaphylactic episodes. So we were able to establish that diagnosis, and then eliminate exposure to the ingestion of mammalian meat which eliminated the anaphylactic events.

DR. CAUDLE:
Are there any different considerations for serum tryptase testing in a patient with an anaphylactic reaction to a known trigger, such as beestings?

DR. LIEBERMAN:
Any patient, and that includes all patients with that disorder, must have a serum tryptase. It's ideal to get that serum tryptase during the event, but if one doesn't one should allow for a few days to go by, and then repeat a baseline serum tryptase. Why? Because of the fact that a very significant number of patients who anaphylax to insect sting will have an underlying mastocytosis or hyper alpha tryptasemia. In fact, patients with hyper alpha tryptasemia have an increased incidence of mastocytosis and increased incidence of idiopathic anaphylaxis, and an increased incidence of anaphylaxis in general. That’s one of the cardinal manifestations.

The measurement of a serum tryptase semiquinone, for the evaluation of anyone, who has an allergic reaction to, a, insect sting of any sort. Hymenoptera stings, yellowjacket, bee, hornet, wasp, or fire ant stings, which we have a lot of here in the south, all of these patients must have a serum tryptase. The reason that they need a serum tryptase is first of all to evaluate the baseline serum tryptase, because how we desensitize a patient and how we follow them, and the treatment that we give them is greatly dependent upon the level of baseline serum tryptase.

And secondly, anaphylaxis can vary in severity frommild to fatalities. And there are certain risk factors which identify those patients clinicallywho are at risk for severe reactions. ~~F~~or example, males are more severely affected by insect sting reactions than females. Number two, the level of baseline tryptase; the higher the level of a baseline tryptase, the worse the event. Number three, the presence of hives is a good modifying factor. That is, if a previous event was characterized by urticaria, then future events are to be less likely to be severe. And the importance that takes is that people who show the risk factors and especially people with high levels of tryptase present a risk to the desensitization process. That is, the immunization of peopleinsect venom.

DR. CAUDLE:
And what role does serum tryptase play in the ongoing management of patients who have anaphylactic reactions to insect venom?

DR. LIEBERMAN:
The serum tryptase is a marker for severity of anaphylaxis. So it's a risk factor. All patients with anaphylactic events due to mastocytosis should be monitored for their serum tryptase. they should be treated with great caution when that serum tryptase is elevated.

Any patient experiencing a reaction should be desensitized. it is the treatment of choice. And when one does this, those people who had the risk factors identified, that is, ~~uh,~~ the presence of hypotension, male sex, for example, the absence of urticaria, and high tryptase elevation must be treated, for lack of a better term, more gingerly. The desensitization process is conducted with great care, because of the incidence of anaphylactic events in these individuals~~,~~ is not only more frequent, but these events are more severe and can be life threatening. ~~I~~t's no excuse to discontinue the immunization, because it's the only way to protect the patient. It's just that we have to do it with great care.

DR. CAUDLE:
And Dr. LIEBERMAN, are there any key take-home messages you'd like to share with our audience?

DR. LIEBERMAN:
Oh, I have a million. I wish I had time to do them all. YesI would share with you, firstand most importantlyis that it is quite clear that serum tryptase is underused. We have no doubt about that. And looking at the world of serum tryptase from the standpoint of an allergist especially a particular interest, in anaphylaxis one sees every day lost opportunities chances of having been able to make a diagnosis definitively. So it would make ,my job so much easier if all the indications we have talked about for the measurement of serum tryptase were utilized.

I would also like to call attention to this new disease of hyper alpha tryptasemia, because a brief word about its pathogenesis is so exciting, that I can't lose the opportunity to mention it. If one thinks about why you have a serum tryptasewe know it's not there to hurt anyone, but teleologically, it must have a function. And the function appears at least based on known animal models, to enhance anaphylactic events. This has not been demonstrated in human beings to date. But based upon the enzymatic activity of serum tryptase we can certainly postulate reasonably that enzymatic activity is active in making events worse. And the reason that that's important is that it appears to be the explanation behind the great heterogeneity of symptoms in, hyper alpha tryptasemia.

It has been clear that in this condition, there is markedly elevated tryptase activity due to the presence of heterodimers due to the presence of combination of alpha and beta tryptase. And now, we have at least a tentative explanation of why people with an elevated copy of a gene for alpha tryptase can have such a plethora of varied symptoms.

And the last thing perhaps, if I had another important point please, when you see patients who are having an acute attack, remember that 90-minute window that you have to draw serum tryptase and go ahead and definitively establish a diagnosis at that time.

DR. CAUDLE:
Well, thank you so much for joining us and your points were really a great way to round out our discussion on serum tryptase testing. I'd like to thank you, Dr. Phil LIEBERMAN, for helping us better understand the role of tryptase testing in chronic mass cell disorders and anaphylaxis. Dr. LIEBERMAN, it was great speaking with you today.

Dr. Lieberman
So I thank you very much for giving me the opportunity out of, stating these things this morning.

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