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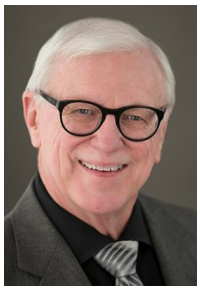
Transcript – Coag Conversation

Immune Thrombocytopenic Purpura (ITP) and the Inherited Platelet Function Disorders

Conversation #1: Mechanisms and Clinical Presentation of Childhood and Adult ITP

Featuring:



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Transcript of the Conversation—Part 1:

Mr. Fritsma: Hello and welcome to Coag Conversations, an educational series sponsored by BioMedica Diagnostics of Windsor, NS, Canada.

Our topic for this series is Immune Thrombocytopenic Purpura, ITP, and the Inherited Platelet Function Disorders.

I'm George Fritsma, faculty for the University of Alabama at Birmingham School of Medicine Division of Laboratory Medicine and proprietor of the Fritsma Factor, Your Interactive Hemostasis Resource.

It's my privilege to introduce our guest, Dr. Michele Lambert. Dr. Lambert received her undergraduate degree in Biology from Rensselaer Polytechnic Institute and attended medical school at Rutgers University. She did her residency in pediatrics at St. Christopher's Hospital for Children in Philadelphia, followed by a year as Chief Resident and then Hematology-Oncology Fellow at the Children's Hospital of Philadelphia, often shortened to CHOP.

She is now an Associate Professor of Pediatrics in the Pearlman School of Medicine at the University of Pennsylvania and a Pediatric Hematologist at CHOP, where she is the clinical director of the Special Coagulation Laboratory and co-director of the Frontier Program in Immune Dysregulation as well as the director of the CHOP Pediatric Platelet Disorder Program. Her particular clinical interest is in the inherited and acquired platelet disorders and in the interplay between genetics and disease. Her current research focuses on understanding the role of genetics in this space. She is a member of the ClinGen Hemostasis and Thrombosis Clinical Domain working group and a Co-Chair of the ClinGen Hemostasis and Thrombosis Gene Curation Expert Panel as well as the past chair of the Pediatric ITP Consortium of North America.

By understanding the drivers of differences in biology in platelet disorders, Dr. Lambert hopes to develop targeted therapies to improve outcomes.

We'll begin today with a review of the mechanisms and clinical presentation of childhood and adult ITP. Welcome, Dr. Lambert. Let's begin our conversation with your comments on the clinical prevalence of pediatric and adult ITP.

Dr. Lambert: Thanks. And thanks for that very kind introduction and thanks for having me here. So pediatric and adult ITP are both rare diseases. And ITP is a "funny" disease. It has gone through a couple of name changes over the years and we actually now know that it's immune mediated and that not everybody has purpura. So, I think many people now just call ITP Immune Thrombocytopenia and have dropped the purpura from the name and just left the ITP acronym, because we can't change acronyms, that just makes people a little bit confused. But I think a lot of people now just refer to it as Immune Thrombocytopenia. Recognizing that not everyone develops the purpura that was classically associated with the disease that was described back in the 1300s.

So, ITP is a disease that occurs both in childhood and adults. It occurs in about one in 20,000 children and it's similar in adults. It's about 1 to 4 in 100,000 adults, so the prevalence is similar in adults as well. But there are a couple of different age peaks. So we see that there's a little bit of a peak in the preschool age to early school age childhood group of children and then it sort of goes down a little bit and then again in adolescence it goes back up. And then there is a little bit of a drop, but not too much and it sort of is steady through adulthood and then goes back up again when you get to be over about 60 years old. There's another peak and it goes back up again. So that older adults, there's a third peak and there's a little bit of a shift between males and females as well. So, in young children, it's just ever so slightly more prominent in males, with a ratio of about 1.2 to one and then in adolescence it flips and is a little bit more prominent in adolescent females than in adolescent males. By the time you get to be a young adult, it's a little bit more even. There's a little bit of a flip then as you get to be an older adult in childbearing age, it's more prevalent in women and then in the older adults, it's a little bit more prevalent, again in men.

Mr. Fritsma: Oh, that's interesting. I thought the prevalence was higher in women than men throughout older adulthood, so that's a little different than the notion that I've had. Another notion I've had, or perhaps from experience, knowing people with ITP, that the diagnosis in the past has been pretty much a death sentence. It was a slow but ultimately fatal disorder, and it seems as though now that's not quite true anymore.

Dr. Lambert: That's correct. I think we now have a lot of different therapies for primary ITP and so the landscape of the disease in adults has significantly changed. And it's a chronic disease because we can't really, we're still not very good at making it go away completely. But it's definitely much more manageable than it was. And the risk of bleeding in treated ITP is less in the adult population.

In pediatrics, it's a very different disease because the majority of children actually will resolve. So, over 80% of children will get better from their ITP spontaneously, whether or not we intervene early on with immunosuppressive therapies like steroids or IVIG [intravenous immunoglobulin therapy] or anything like that. And so whether or not we treat your ITP early on, most children will get better and so we often don't treat ITP in childhood because they're going to get better and they don't usually have a ton of bleeding symptoms that we need to do very much about. So, it's very different compared to adult ITP.

Mr. Fritsma: So, in terms of both pediatric and adult ITP, what are the clinical outcomes? It used to be…I remember that an ITP diagnosis in adulthood usually meant a fairly slow, but chronic disorder that ended as a fatal disorder. Is that still true?

Dr. Lambert: No, I don't think so. I think you know now we expect adults with a diagnosis of chronic ITP to have a pretty good outcomes. They may need to be on therapy in order to maintain a better platelet count and have decreased bleeding symptoms. But most adults who are diagnosed with ITP now will have some therapy that is effective. And are able to keep their platelet count up and they're able to maintain pretty active, relatively normal lives.

Mr. Fritsma: And with children, it's usually a disorder that ends after a while—it doesn't progress. Is that so?

Dr. Lambert: Yes. So, the majority of children will have self-limited disease. So, most of the time I will tell parents when I meet a child for the first time with ITP that in between 70 and 80% of children, we see resolution of their ITP. The majority of children will resolve in the first six months. Another group of them will resolve between 6 and 12 months and then there's still some kids who will get better even after that 12-month mark. And will continue to have some kids who resolve, you know, at 12 months. Will continue to have some children who resolve at two years, at three years, at five years post diagnosis. But there is not a time frame at which point we say, oh, you're never going to get better. Because we know that that ITP might go away even once they become a young adult. And so we know that that ITP could still go away.

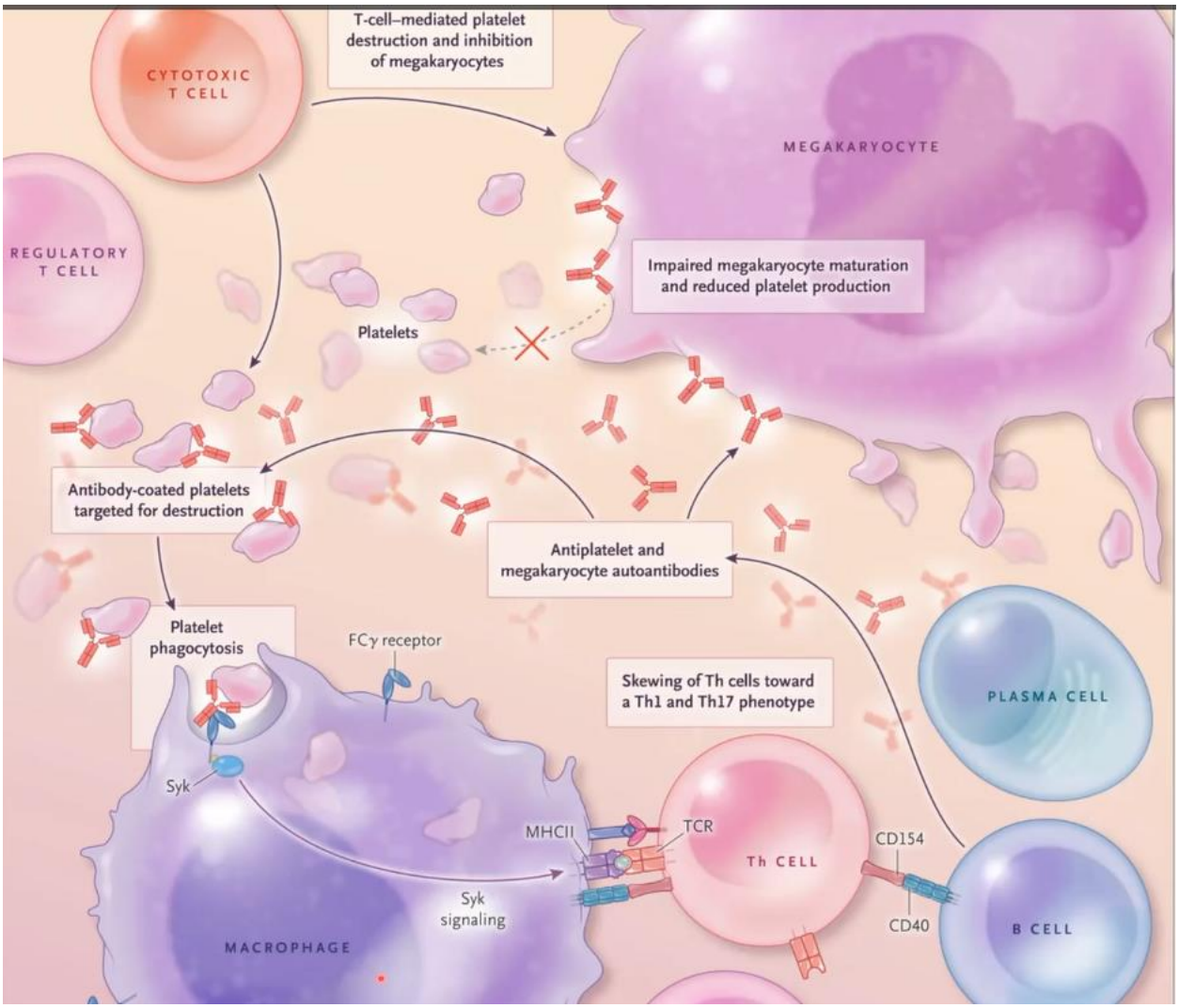
Mr. Fritsma: Thank you, Next month we'll talk a little bit more about laboratory tests, but what kind of platelet counts are we talking about that define the condition and dictate the treatment?

Dr. Lambert: Yes. So, in defining ITP, we say that in order to have a diagnosis of ITP, you need to have a low platelet count. And we say that platelet count should be less than 100,000. Recognizing that a normal platelet count is a platelet count that's over 150. So, you have this population of patients that fall between 100 and 150. Technically, they wouldn't meet criteria for ITP in general. But the majority of patients at least, certainly true in the pediatric population, and I think more and more we're recognizing that this is also true in the adult population who truly have ITP and have immune mediated thrombocytopenia and not some other cause for their thrombocytopenia will actually have severe thrombocytopenia with the platelet count of less than 20,000 at some point during the course of their disease, and that's really pretty characteristic for ITP.

And that platelet count tends to vacillate and go up and down. And that's also rather characteristic of ITP and not a lot of other types of thrombocytopenia. So that if you have a patient who has severe thrombocytopenia and then the platelet count gets better and then they have a viral illness or something else happens and then their platelet count drops back down again. That's really quite characteristic of a patient who has immune thrombocytopenia and not so much characteristic of the inherited thrombocytopenia.

Mr. Fritsma: Thank you. That is interesting. Let's talk a little bit about the mechanism. My knowledge about ITP is that the mechanism is you get an autoantibody and that's it. But I've been looking at some of your materials and others and I find out that's not quite true. So, could you go into the mechanism for ITP both in kids and adults?

Dr. Lambert: Yes. So, one of the reasons we call it immune thrombocytopenia, it used to be called idiopathic thrombocytopenic purpura. But now we call it immune thrombocytopenia that we know that it's immune mediated in patients who develop this disease. And it is all parts of the immune system that are dysregulated. Let me pull up a figure quickly to show the different ways in which the immune system can be dysfunctional in patients who have ITP.



Dr. Lambert: So, in the past, we always recognized previously that there was an autoantibody-driven process that was important for ITP. And here we could see there is certainly an auto antibody component to many patients who have ITP. And you'll get auto antibody coated platelets and destruction of those platelets typically by macrophages that reside within the spleen of patients who have ITP. This is why splenectomy is so effective in many patients who develop ITP and it still can be an effective therapy, particularly for those patients who are looking for a treatment where they don't need to worry about taking a medicine every day for their ITP. And so, auto antibody coated platelets taken up by splenic macrophages is a mainstay of the pathophysiology of ITP.

However, we know also that those antibodies can attack the megakaryocytes that reside within the bone marrow and cause destruction of the megakaryocytes and interfere with megakaryocyte function and release of platelets. So, there is a relative inability of the bone marrow to respond to that low platelet count and to make enough platelets to be able to continue to support thrombopoiesis in the setting of ITP. And this is why the thrombopoietin receptor agonists have really been such a game changer in this disease and have been so effective is because there really is a megakaryocyte defect in patients who have ITP as well.

And so, by giving thrombopoietin, we can increase platelet counts in a lot of our patients who have ITP. We know too, that in addition to there being a problem with the B cells, which are the parts of the immune system

that make autoantibodies, you can have some patients who develop plasma cells so there are resident B cells, long lasting B cells basically, antibody producing cells that stay and persist. So even if you remove their B cells those plasma cells will continue and live on and continue to make antibodies. So, for some patients, we really need to intervene and stop the plasma cells from making antibodies.

Dr. Lambert: And then in some patients, the ITP really seems to be more of a T cell driven process. So, the T cells are the parts of the immune system that classically are important in the immune response against viruses, They support B cells and they support macrophages and they make cytokines in order to help support the immune system. And you can have T cells that are cytotoxic that typically would take out viruses, but instead, they learn to destroy platelets and / or even attack megakaryocytes in the bone marrow in some patients who have ITP.

And in some patients we have a change in the ratio of helper cells. So, they're really overactive and they're driving B cells to make more antibodies or they're driving macrophages to be more active and take up more antibody coated cells.

Or, we get a loss of regulation of other T cells like the cytotoxic T cell or the T helper cell and you're not able to regulate those cells normally so we have a regulatory T cell defect. So we know that all of these different immune mechanisms need to be carefully balanced to have a good functioning immune system and in ITP we've certainly seen that in some patients all of those different parts of the immune system can be dysregulated and broken and cause trouble and lead to the development of ITP.

Mr. Fritsma: So, it's just the macrophages that recognize the coded platelets and that's the mechanism that causes it to clear. Is there any other mechanism that that causes the clearance of the platelets besides that?

Dr. Lambert: So cytotoxic T cells can also clear platelets. And cause the destruction of platelets as well directly. So that's another mechanism of clearance of the platelets. And there's also now an evolving story of liver macrophages and liver Kupffer cells that may also play a role in helping to define which platelets are destroyed and taken out of the circulation as well. So, the liver may also be playing an important role in helping to regulate the platelet count in ITP patients and also in normal physiology too.

Mr. Fritsma: Well, it's a lot more complicated than I thought, and I suppose that leads to more research and therefore more ways to treat the disorder as well. And I have one last question that occurs to me. It seems like a lot of the mechanism work that's happened is because of COVID. There's just so much mechanism work that's happened at that time. Has the COVID pandemic provided additional information for ITP or has most of this information come from before?

Dr. Lambert: I actually think that a lot of the immune stuff actually started before the COVID pandemic hit. I think that as a result of the COVID pandemic, we spent more time thinking about what is the best way to treat a patient without impacting the immune response or minimally impacting the immune response. Because we were worried about making sure that we didn't cause harm in other ways that maybe would have unintended consequences. And so, I think when we had been using lots of rituximab to take out the B cell component and stop the antibody production in patients who have ITP prior to the pandemic, once the pandemic hit, I think many providers started to stop and think and say do we really want to turn off antibody production for six months, or more, in some patients? When we know that there's a global pandemic happening right now and maybe they're going to need to be able to respond to an infection. And so I think there was a lot of hesitancy to use rituximab in that setting. And to try to treat ITP in other ways that maybe didn't have such a long duration of effect, so you could turn it off.

Mr. Fritsma: So really COVID made the whole thing more complicated to treat.

Dr. Lambert: It did a little bit but also opened a lot of new ways of treating ITP because people then were like, well, let's see, does this therapy that we use in other autoimmune diseases, does this therapy work? Can we see a response in ITP? And there's some preliminary data from some patient populations that suggest that this part of the immune system may be playing a role. And I think it all sort of came together and people started to put together other clinical trials.

Mr. Fritsma: Well, thank you for that. That was very interesting. Let's just go back for a moment. Have we seen very many cases of childhood ITP that really do become chronic and extended to adulthood? Or do does it always resolve?

Dr. Lambert: There are some children who will continue to have ITP even once they become an adult. It is rare, but not unheard of for childhood ITP to continue through all the way into adulthood. But it is quite unusual and if a child has ITP that's diagnosed particularly early in childhood, like preschool age, and they get to be a young adult that still has ITP, I question that ITP diagnosis. And I would want to know is there something either driving that immune response, something going on with the immune system that's making that person continue to have ITP, or is there actually an underlying inherited platelet disorder that maybe, looks like ITP but actually isn't ITP ? And that that patient perhaps doesn't really have ITP.

But I have had a couple of patients where we've really looked for everything else that that continued to have ITP at least into young adulthood. And I certainly have met some families, or some patients rather, at some of the ITP patient meetings who were diagnosed in childhood and continue to have ITP as adults. The majority of those patients, though, were not young, young children. There are a few, though there are a few.

Mr. Fritsma: Which will lead to the discussion in the third conversation that we have about inherited platelet function disorders, which perhaps are a little more prevalent than most of us believe. And leads to a lot of new laboratory work that will come on too. So, we'll look forward to that.

Well, this concludes our first conversation. Dr. Lambert, thank you for your expertise.

We encourage participant questions and comments, and there's a link on the BioMedica Diagnostics website for you to not only see the webinar, but to download a transcript of today's talk. And you can forward your own questions or comments.

Please join us next month for conversation #2 that's entitled Laboratory Diagnosis and Management of ITP. Thanks to BioMedica Diagnostics for sponsoring Coag Conversations, and thank you for your participation.

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