

Common Variable Immune Deficiency (CVID)

00:00 Hello, and welcome to Primary Immunodeficiency Questions and Answers. This podcast is a service of the Immune Deficiency Foundation, a nonprofit organization that improves the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency.

00:17 Primary immunodeficiency, or PI, is a term used to describe a group of more than 400 rare, chronic disorders in which part of the body's immune system is missing or functions improperly. In upcoming episodes, we will explore specific diagnoses so listeners can gain a better understanding of the symptoms and treatment options of these diseases.

00:40 And now, let's begin.

(Music)

John Boyle: 00:51 Hi everyone. Welcome to this episode of Primary Immunodeficiency Questions and Answers. I'm your host, John Boyle.

01:00 Common Variable Immune Deficiency, or CVID, is just one of more than 400 primary immunodeficiencies. It is one of the most frequently diagnosed primary immunodeficiencies, characterized by low levels of serum immunoglobulins, or antibodies and a loss of antibodies, which causes an increased susceptibility to infection. While it is considered "common" compared to other immune deficiencies, questions still remain about the diagnosis, treatment, and well-being for people living with CVID.

01:29 Today's guest is Dr. Charlotte Cunningham-Rundles. Dr. Cunningham-Rundles is the David S. Gottesman Professor of Immunology at the Mount Sinai School of Medicine in New York. She is a Professor of Medicine and Pediatrics, a member of the Immunology Institute, directs the Immunodeficiency Clinic at Mount Sinai and is a member of the IDF Physician Advisory Committee. Dr. Cunningham-Rundles is an expert in more than 400 forms of primary immunodeficiency but she has a special interest in CVID.

01:58 Thank you so much for joining us today, Dr. Cunningham-Rundles.

Dr. Cunningham-Rundles: 02:03 Well, thank you, John, for inviting me to talk about this rather complicated disease.

John Boyle: 02:08 It's great to have you here so let's dive right in. Can you give us, beyond those two sentences or so that I already gave you, a real brief description of CVID? And especially, wanting to explain the fact that it's called common when it's arguably not.

Dr. Cunningham-Rundles: 02:28 I think that's largely the historical perspective was that some of the first immune deficiencies ever recognized were really rather rare, in fact, perhaps one in every several hundred thousand infants oftentimes and I think people were originally rather stunned to learn that there were some who adults who were older than infants who then also were immune deficient in similar ways. So, I think that's part of the reason that it still stuck with the name common. In terms of how you define it, that turns out to be something which is relatively important because you end up wanting to be sure that a person that you are describing as having an immune deficiency has really a clear cut loss of both the gamma globulins, IgG and the other antibody which is IgA and oftentimes, the lower levels of IgM as well. Those are the serum gamma globulin levels.

03:25 But going along with that as you said a second ago, you also have to show that that person really does not have protective antibodies, again, such common things as measles or mumps or chickenpox, for example, or tetanus. So the evaluation includes not only the levels of antibodies but also, you have to go and make certain that even after an immunization, a person still fails to respond to that vaccination and it's important to be rather sure in the beginning whether this is really the case. You don't like to diagnose a

person with immune deficiency unless you really have pretty much as much information as you can really in your medical record.

John Boyle: 04:08 Well, that's very helpful but one of the things that I think we see and we hear from members of our community is a bit of confusion about some of those issues of antibody levels, about their response to vaccines and whether they have or whether their physician thinks that they have CVID versus Hypogammaglobulinemia. Can you talk a little bit more just to help separate out what Hypogammaglobulinemia is, is and is not considered versus CVID? How do they interrelate, where do they overlap and where are they distinct and different?

Dr. Cunningham-Rundles: 04:47 Well, technically speaking, Hypogammaglobulinemia would simply be the term that you put onto a patient's record, in whom the level of the total amount of gamma globulin was subnormal. And so, in a way, that's kind of like the generic term for all the defects of the immune system where antibody or the lack of those gamma globulin molecules is too low and that would give you a chart definition, I would say, of the gamma globulin levels being low. So that would be the "hypo" which means too little of and then "gammaglobulinemia" would be, you know, the rest of that term. So that's kind of like the overarching biggest term but then you need to sort of dissect that down - alright, why is that person Hypogammaglobulinemic?

05:39 A person who has, for example, a very very significant gastrointestinal disease might lose some of the gamma globulin, for example, in the diarrheal fluid, and that would give a person Hypogammaglobulinemia, but the functions of the antibodies is still perhaps not really impaired. And so, the next thing that you generally do is say, "Alright, the levels of gamma globulin are low, but what is the quality"? It's a question of the quality and the quantity. And to do that, then you would go and check whether or not some of those protective antibodies that we all presumably possess, whether those are in levels that are considered to be in that protective zone or not. So, I know it's a bit confusing to have so many terms.

06:27 The other thing is that I think it's true that you have to confess that it's very easy to decide when a person is Agammaglobulinemic, and that means there is no gamma globulin at all and then a person who has very normal levels, that's very simple, but then making a decision about a person who's levels are half normal. Alright, is that Hypogammaglobulinemic or not? Is that going to qualify you for the diagnosis of CVID or not? That's when you really have to check out the function a lot better because you could have a level which looks as if it's say half normal. On the other hand, there could be no good functioning antibody contained in that serum protein. On the other hand, you could have a person who's levels are relatively low and yet, every antibody that you're trying to find is actually still present. So I won't be so bold as to say that it's extremely easy to decide where that person's immune deficiency ranks. Is it very severe or mild or moderate or perhaps, almost so slight that it would be hard to even detect?

07:39 And so physicians vary quite a bit about where they actually put the marker of Hypogammaglobulinemia or Common Variable Immune Deficiency. I think most of us would end up wanting to apply that diagnosis when the IgG level is quite sufficiently low, less than half, generally. And in addition to that the quantity, the quality of the antibody is also really not holding up. Admittedly, it's not something every physician will completely agree upon.

John Boyle: 08:11 So, with what I'm hearing and with what I understand of it and want to make sure that I am in fact clear and that our listeners are as well: So to that point, everyone who is diagnosed with CVID or Common Variable Immune Deficiency is ultimately someone who has Hypogammaglobulinemia because again, that just refers to the low levels of IgG. So everyone with CVID has Hypogammaglobulinemia but not everyone who is diagnosed with Hypogammaglobulinemia would necessarily fit the maybe more specific criteria of CVID or some other form of PI.

Dr. Cunningham Rundles: 08:50 I think that's basically correct. Also, remember that you would want to use the name Common Variable Immune Deficiency as a term that suggests that this is a condition that

person is likely to have been born with and that it will be a condition that will persist. And Hypogammaglobulinemia could occur for example in a patient who is given some therapeutic treatment which lowers the gamma globulin level quite purposefully due to a treatment, for example, for a cancer treatment or perhaps for, another reason of treating an autoimmune condition. The Hypogammaglobulinemia might be there for a while, in other words, it would not be a permanent condition.

09:35 So we rather dissect the two that way as well. One would be almost drug-induced or disease-induced and the other is one where you're genetic constitution stipulates, you know, you just don't make enough of this functioning material.

John Boyle: 09:52 Now, I appreciate you making that distinction because we, of course here at the Immune Deficiency Foundation, focus primarily on primary immune deficiencies or those that are genetic or intrinsic as opposed to other immune deficiency situations where it's caused by essentially a secondary cause. But of course, that links to something that you invoked yet another important term: autoimmune and a number of people, many within the CVID world, are known to have an autoimmune condition or multiple such as ITP, Hashimoto's, Crohn's, Celiac, along with their CVID. They have not just the immune deficiency, but an autoimmune condition that is operating alongside of it. Can you talk a little bit about this overlap of symptoms, diagnoses and this world between immune deficiency and autoimmune, especially as it relates to those that you see with CVID?

Dr. Cunningham-Rundles: 11:00 Well, what you say is completely right and in about, I don't know, somewhere between 40-50% of the patients that I see, and that's probably a little bit higher than I think, perhaps, the real average would be if you took every patient with Common Variable Immune Deficiency in the United States, but about 50% of my patients do have an additional, what you might call, autoimmune or inflammatory complication. It does seem to be hand in glove with the fact that your immune system is really not capable of making an antibody to, for example, tetanus or pneumococcal vaccination. On the other hand, for some reason, it doesn't seem to have a problem making an antibody to your red cells, platelets, for example, or neutrophils or some other cell of the body.

11:47 That's one of those things that is part and parcel about the way the immune system works is it has to figure out what is a self-antigen and what is an external antigen. An antigen being a foreign protein or a foreign substance like a virus or a bacterial cell. And that's, unfortunately, one of the common messages in our patient population, which is that not making the proper antibodies, one occasionally then just simply makes antibodies against internal tissues. We don't completely understand that but there are many, many molecular reasons why that's the case. It's a subject of tremendous amount of research, actually, as to why that might be the case.

12:30 Sometimes, it's a genetic problem. I would say, more often it's having to do with perhaps continuous bombardment with bacterial substances that the immune system really can't handle very well and for that reason, you know, an external or an abnormal response then perhaps develops as a result of that. But it is one of the concerns of doctors taking care of Hypogammaglobulinemia is to try to think of ways to ameliorate those conditions with as least immunosuppression as one can manage to use.

John Boyle: 13:07 Now to switch over to a - what is maybe a little bit of a tricky question to answer here - Can you tell us about what is known, observed within your own professional experience about the inheritance of CVID? Certain forms of PI have a very specific and known pattern of inheritance because maybe there's a single gene involved and you can track whether it is recessive or dominant and X-linked or not, but with CVID and this way of diagnosing it in the reasonably broad category, that seems somewhat tricky. We do hear from people at our events that we put together, that there are some people who are diagnosed with CVID who have other members of their family who do and then others who don't but are concerned because they really don't know much about what can be done to test or what to expect in the future, so inheritance and CVID, what are your thoughts?

Dr. Cunningham-Rundles: 14:13 Well, I used to say and when I was looking at all the records of the patients that I've seen with CVID over time, that the chances of another family member being affected is perhaps less than 10%. Those numbers have usually held up fairly well. The confusing part about that is that, now, currently using much more modern methods of genetic diagnosis, we actually now are able to put a name onto the immune deficiency, at least of the patients that I see, somewhere around 20-25% of the time. So you might wonder, how do those numbers square?

14:56 If 25% of my patients have an immune defect that I can put my finger on, saying this is the genetic reason, why is it that perhaps less than 10% have another family member that we know about? That's a tricky question because of course, not everyone has an available family member to test, not every Hypogammaglobulinemic or CVID patient has a child that I can test, but when I have been able to do that, then you'll discover that you have the diseases that are the commonest. The genetic reasons in the United States, are what we call the autosomal dominant genes. You might say, dominant? Dominant sounds as if that should, if you have the gene, then the disease should immediately be present.

15:48 That's really contrary to what we actually find, which is, although the gene is considered to be a dominant gene, in another family member you'll discover that that gene actually is present but on the other hand, it's not activated. That's something which is the topic of a lot of research. Why would a gene which is present not raise its hand and be obvious? We find that repeatedly for these autosomal dominant genes is that sometimes although we call them dominant and you may be able to trace them in families, not a small number of times you also find that it is not expressed. Perhaps because the immune system has so many ways to exert its authority, there's another gene which is lurking in the background which also has to have been present in order to make this more obvious.

16:44 But again, that's a bit of a speculation because we honestly don't really understand why if these genes are dominant, we don't see many, many more families affected. That is my experience is that infrequently, less than 10% of families will have a mother, a father, or a child who is affected. I think that's useful for families that are considering having children. We do use genetics quite a bit and I think that having a genetic piece of information is very useful for projective parents. It's also quite likely that, in the first place, we will not find the gene. As a matter of fact, it must be 80% against going by the current rate of 75-80% against, number one. Then number two, even if the child inherits the same gene, does not mean that that child will eventually even become immune deficient. So it's a very, much an area of ongoing research as to unravel why it is that we don't see more, at least in the United States.

17:53 Now, in other countries with other genetic inheritance patterns, it's much more common where there has been, for example, more cousin marriages, for example, or more people have been related in the same family who have gotten married, which is more common in other populations than in the United States.

John Boyle: 18:14 Well that is- it is a tough question to pin down in terms of the answer because, of course, what is still under research but I really do appreciate your kind of giving us that anchor in people's minds if nothing else for dealing with that issue because of course, it is one of the questions for people who are planning for families or waiting to see if it pops up in other branches of their family so that is greatly appreciated.

18:45 Well, that sounds like a perfect point for us to both take a deep breath and so we are going to take a break here and we will be right back in just one moment.

(Music)

19:01 No matter where you are along your journey, IDF wants to help you manage living with primary immunodeficiency or PI. As a community empowered organization, IDF can provide you with support, education, and resources to help you cope with a wide variety of issues related to PI, including physical and mental health, insurance, and relationships. For more information, please visit: www.primaryimmune.org.

(Music)

John Boyle: 19:35 Welcome back. My guest, Dr. Charlotte Cunningham-Rundles is discussing the symptoms and treatments associated with Common Variable Immune Deficiency or CVID. Thank you so much for sharing your thoughts with us thus far but we are going to switch gears here and talk a little bit more about the health management side for those living with CVID.

19:53 We've talked about the definition and the sort of presentation of CVID, we've talked a little bit about the inheritance, but now, let's talk a little bit about the treatments. Now, of course, anyone listening to this podcast who has CVID will know a fair bit about that but to level set, both for them, as also for anyone else who is interested in CVID who's listening, can you talk about when you diagnosed someone with CVID, when they come to you, what are the primary treatments that come into play to help address what it is that they are lacking?

Dr. Cunningham-Rundles: 20:36 Well, of course, the mainstay of therapy as you are just now alluding to, of course, is to get adequate levels of gamma globulin protection into the blood. That could be by intravenous or subcutaneous methods. Fortunately, there really are quite a number of extremely effective products now in the United States and elsewhere, of course, in the world that are, I think, more and more tailored to the individual patient. Both intravenous and the subcutaneous forms are really the similar degrees of efficacy. There really is no difference between the two. I think what one wants to do is to make it as least impactful on the patient as possible, so the most expeditious methods and those that fit into that person's life the most conveniently are going to be the ones that are the best to use.

21:32 So that's kind of the mainstay of therapy is making certain those antibody levels are quite, quite satisfactory. Everyone uses gamma globulin slightly differently so it's also a very reasonable thing to do and I know that we do that here. We do measure gamma globulin levels perhaps every 6 months, certainly every year, just to make sure that that person is adequately dosed. We had found something quite interesting to me which was that we obtained a very large data set from a homecare company across the United States. One of the things that came out of that study was that, in the United States, a patient tends to, of course as we all know, gain a bit of weight over time and that means that, in fact, the adults, the older that they got in this study, the less gamma globulin they were getting in terms of the number of milligrams per kilogram of body weight. It seemed to us that that was because the doses were no longer being calculated on body weight in many of the adults as they were in children. Pediatricians are so used to using body weight. Internists, you know, are less used to doing that. They tend to stick with a dose they've always been on. We found that was quite interesting that perhaps some of the older adults were getting less than, you know, the children were. That probably is not a very justifiable dosage, I would say, in some of the older subjects that we saw in that report.

23:16 So, with regards to antibiotics, of course, that's the second mainstay of our therapy. We use antibiotics, of course, for acute infections but we also use antibiotics rather liberally also for prophylactic treatment, not only in the children but sometimes also in the adults. Those might be, for example, common antibiotics in use would be the Trimethoprimselfa, for example, the Azithromycin or some of the other common Macrolide antibiotics might be used. I should say that one of the common themes about patients with Common Variable Immune Deficiency if you might put it that way, is the type of bacteria which are the most likely to occur are generally organisms of relatively low virulence. That, of course, means that the choices of antibiotics are still relatively broad and generally, reasonably easily handled as well from the standpoint of just simply taking that antibiotic and having rather few side effects.

24:23 So those are the first two mainstays, the gamma globulin, and the antibiotics. Then of course, as you were saying a moment ago, when we have the inflammatory complications, then, of course, we're on entirely new ground. In those cases, we will use many of the therapies that are in-use amongst our colleagues. For example, for very low platelet counts that persist, we might use the rather commonly used

monoclonal antibody, Rituximab. That's been shown to be really remarkably successful in treating low platelet counts in patients with Hypogammaglobulinemia. I will make one other comment about that too: We do generally try very hard to avoid splenectomy, in case that question every arises. Generally speaking, one doesn't usually need to do that procedure which was so commonly done in the past for low platelet counts, but nowadays I think there are ways to get around that with some of the additional therapies such as Rituximab. There's also additional therapies that have been used to raise the platelet count. Additionally, therapeutics that our colleagues are using and we, of course, in the world of primary immune deficiency, are always eager to have our colleagues come up with additional therapies that we can adopt for our own uses and our own practice.

John Boyle: 25:47 Well, you mentioned a moment ago, your colleagues and especially with the CVID patients who have an autoimmune or an inflammatory disorder or maybe something that is seemingly unrelated to this, the issue of, if you will, balance of having maybe a number of different medications, a number of different therapies, maybe a couple of different specialists who are involved. Not just the immunologist, who's more focused on the primary immunodeficiency side, but maybe the hematologist who's focusing more on the ITP or any of the other number of "ologists" who might be involved. How do, either you coordinate at Mount Sinai or what is the ideal for a patient or a patient and a provider such as yourself to try to coordinate that care and to make sure, again, the one treatment for the one side of their maybe co-morbid situation, is not further complicating the others because people struggle with the side effects of any number of therapies or medications. With those sort of situations, how do you and your colleagues approach it?

Dr. Cunningham-Rundles: 27:01 Of course, that's always very difficult. I think the best answer is one which is perhaps not readily possible everywhere but I think one tends to develop a small team of physicians that are in your area, for example, your go-to hematologist, your go-to pulmonary doctor, your go-to gastroenterologist who has previously worked with you on other cases. As you are really getting at here, other specialties are not very familiar with Common Variable Immune Deficiency, to be honest. At a large major medical center, it could be that that's easier, but I think over a long period of time, a practitioner such as myself or a physician who's working in another larger medical center, most likely is developing a small team, I would say, a team approach where you know that that person has previously seen a patient of yours and is not, for example, likely to start to order therapies that are not perhaps the wisest choices for an immune deficient patient. For example, large doses of steroids or other immunosuppressives, we would tend very much to use less, I would say, and less frequently as well.

28:29 My major colleagues here at Mount Sinai are the hematology team, but they have, fortunately, and ourselves we've gotten used to the use of some of the therapeutics for these immune deficient patients and they have gotten very used to seeing patients of mine. This is also true for the gastrointestinal unit and also for the pulmonary unit. I would say these are our major, I would say, sub-specialists that we so commonly need. Very occasionally one needs another physician in another specialty but I think these are the ones that we so often need that you slowly over time, you develop the physicians that you know are going to work with you and will not misunderstand the intrinsic nature of the immune defect.

John Boyle: 29:22 Now let me come back to something that you mentioned earlier which was along the lines of those who are receiving adequate levels of immunoglobulin and then I think the presumption is that they should be doing, in general, quite well in terms of infection control. Can you speak to the patients that you maybe inherit from other providers, people who come to see you? We hear quite frequently from people who have CVID or Hypogammaglobulinemia or something else where immunoglobulin might be used, but they're still getting a lot of infections, and I think there's a question of, on their minds, of "Am I receiving the adequate dose?". How is it that you look at the numbers and the presentation and reconcile what might be the starting dose versus maybe an adjusted dose to make that their quality of life really is what you might expect it to be?

Dr. Cunningham-Rundles: 30:31 Well, there is a range that we commonly suggest for using immunoglobulin - it's kind of a standard amount of 400 to 600 milligrams per kilogram and that's kind of what's written in textbooks and all of the other major references for the uses of immunoglobulin. That, of course, is usually done once per month. If that's going to be intravenous or it's given once a week and if that's that way that's it's ordered, that's also a very useful way to go. So, those are kind of the overall monthly doses, either divided or not divided. Generally, that range is quite satisfactory, but you may have a person who has a lot of gastrointestinal disease and for that reason, they lose gamma globulin as well in the gastrointestinal tract, so you have to actually give them on the higher side of that immunoglobulin dose.

31:29 So, when I am checking a person to find out whether I think they are getting enough, one, of course, is 'how is that patient doing' is very important but then the next thing is 'are they somewhere around 600 milligrams or 500 milligrams over their starting dose or their starting baseline level of gamma globulin'. So, we usually use that as being a way of saying we have really got a full tank here, we have a good full tank. Of course, we like to check at the end, just before the next infusion or the next treatment so that we're sure that we know how low that person might go in the course of a month. I know many people have talked about using gamma globulin and trying to be sure that there is no infections and, to be honest with you, that's actually not possible.

32:21 So, if you look at the package insert of the- all the treatment products will say the same thing. Patients with Hypogammaglobulinemia or CVID, even in the clinical trials that were used to validate the use and the sale of that gamma globulin product, the patients who were optimally treated, in those studies, still have both sinus disease and still have what they recognize as bronchitis. To be honest, you can not expect that that person will end up with totally normal sinuses and you can't expect them to never have a cough again. It's just not reasonable. We're still going to be human beings. We're still living in the world. Sinus disease is not something which is totally conquerable by using gamma globulin. So, I've had patients that were really, tremendously over-treated who came to see me because somehow they still had some sinus ailment leftover. I'm thinking, you know, it's just not going to work - this is just one of those situations where you're going to have to apply either antibiotics or some other treatment for the sinus disease. The sinus is really kind of one of those holdout areas.

33:34 The other one is gastrointestinal disease - it's not going to change with the use of gamma globulin. If a person has GI overactivity and diarrhea, the gamma globulin treatment is just not going to address it. This is true also and you can see this in the package insert, the patient still had some gastrointestinal issues and they still had sinus issues and you can chase it with gamma globulin as much as you'd like but you won't get there. So we use the levels to tell us whether that person is really substantially over the baseline they started with so that we know that we have really got the maximum benefit from that therapy.

John Boyle: 34:16 One area that has been a perennial area of discussion within the CVID groups and at the in-person events that we have, is a sensitive one to some - the use of surgical masks to avoid infection. What do you counsel your CVID patients about in terms of usage of surgical masks versus other practices that may help them to minimize their risk of pathogens when they're in public? What is your take on wearing surgical masks versus all of the other things that one might do that you might recommend to someone who is either newly diagnosed with CVID or is, again, trying to make sure that they are living their life without additional encumbrances?

Dr. Cunningham-Rundles: 35:13 Well that's an interesting question and I have to tell you that I have never counseled a patient with CVID to wear a surgical mask under any circumstances. I suppose I could think of one or two exceptions, for example, if they were visiting someone in a hospital environment with a serious respiratory illness but I would myself probably also put on a surgical mask at the same time. So, you have to go back and take a big step back and say well, patients with CVID, what are they doing?

35:43 Actually, we did a survey on our patients a few years ago and most of the CVID patients that I see or have seen, for example, are either in school, or they're in college, or they're working full time, or they have decided now they're going to retire from their job, they're in their 60s and now they're traveling or they are doing something else that they enjoy. So, to be honest with you, disabled CVID patients are relatively unusual. I have quite a few CVID patients who are lawyers, I have quite a few who are physicians. So, for me to start to suggest that they wear surgical masks would be extremely counterintuitive. So no, I don't suggest wearing a surgical mask unless it might be a circumstance in which I would put on a mask as well. So, for travel, no, I don't think it's required. I could imagine a situation of a person who is themselves feeling very poorly and is setting off on a voyage, you know, for them to wear a surgical mask might be good for everyone around them but I don't see why that person would do it, for example, on an airline.

37:01 I do have patients who tell me they do wear surgical masks, I've had a few tell me that. I don't myself suggest that a person do that. I think it's more important to do the handwashing routine, the 20-second handwashing routine when you're using mass transit or getting off an airline or for example, you're on a bus or a subway but so should we all, most likely. So, I don't have special recommendations for CVID patients, to be honest.

John Boyle: 37:33 Well, just to, maybe take that one step further in that direction, in terms of risk management and you're talking about these patients of yours who have CVID and are in fields that are found with people who are not, are there any areas that you do suggest that those with CVID, your patients, are a little bit extra cognizant about? Anything from how they deal with family and infections versus travel versus any of those issues which may be a topic of conversation. Knowing, of course, that the presentation of CVID can be somewhat broad - there's going to be quite a wide variety but what are the general areas where you do have a discussion about things that they will have to be thoughtful about as they go forward?

Dr. Cunningham-Rundles: 38:28 Well, I pretty much continue to say what I was saying a moment ago is that if you're on these adequate doses of gamma globulin, you probably have more antibody than the person standing next to you. For that reason, you, actually, if you are Hypogammaglobulinemic, you are not extraordinarily likely to develop additional infections unless, of course, that person next to you has a rampant viral infection of some sort and sneezes straight at you. I suppose, you know, there was a study done in, I think it was in Norway a few years ago, a very interesting and lovely study that showed that in a family setting, a viral infection might last longer in a patient who is Hypogammaglobulinemic and occur more frequently than in, for example, the spouse of the patient. So, I think that viral infections certainly do occur but that's going to again be in a family setting is where this particular study was done.

John Boyle: 39:32 Well, I think that that is a fabulous note for us to end on because I think we've really covered a lot of the most important bases. Of course, we could talk about this for days on end but seeing as your time as a clinician and all the other hats that you wear should probably let you get back to what it is that you do. Thank you so very much for joining us, Dr. Cunningham-Rundles. Your insight, your knowledge about CVID and the way that you care for our community members of and engage and help us at IDF is just something we can never thank you enough for. I know that our community, those who are not patients of yours and have not gotten a chance to see you at our national conference or elsewhere will find this really, really useful, so thank you again for sharing your time and your thoughts here with us today.

Dr. Cunningham-Rundles: 40:25 You're very welcome, John.

John Boyle: 40:27 And thank you to all of our listeners for being here with us. We hope you'll join us in future episodes as we explore other forms of primary immunodeficiency. Until then, all of us here at IDF want to wish you good health and strength. And remember: you're never alone. There are always people out there who want to help. We all just have to find each other.

(Music)

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41:16 To learn more about primary immunodeficiency and the PI community, please visit the IDF website at www.primaryimmune.org. And if you have a question you would like answered, e-mail us at info@primaryimmune.org. Thanks for tuning in.