Transcript – World PI Week Talks Season 2

Episode 2 – Treatment & Care

Interviewer/Moderator: Sue Saville

Interviewees: Prof. Frank Staal, Dr. Adli Ali, Stela Andreea Pirvu

00:00:08 Sue Saville

Hello and welcome to the World PI Week talks, a podcast series by the World PI Week, a global movement to raise awareness of primary immunodeficiency diseases, PIDs. This takes place on the 22nd to 29th of April every year.

And in this new season for 2022, we're focusing on the main themes of this year's campaign, which are early diagnosis and newborn screening, treatment and care, health awareness and preventative medicine, and then the latest research. My name is Sue Saville. I'm an independent health journalist and I'm delighted to be hosting these podcasts. To find out more about PIDs, we have the help of scientific experts and patients, clinical organisations and health care professionals.

00:00:52 Sue Saville

We're using the hashtag WPIW talks to promote the campaign. So let's firstly just remind ourselves about PID's. They're rare, but life threatening chronic conditions, and they occur when a person immune system is absent or doesn't function properly.

And there are over 450 different forms of PIDs. And these range in severity, often presenting in the form of persistent or recurring infections, and sometimes leading doctors to treat the infections while missing the underlying cause, leaving the patient vulnerable to vital organ damage and even physical disability, sometimes even death.

Now it's estimated that there are 10 million people worldwide living with a primary immunodeficiency, and between 70 and 90% of people are still undiagnosed. But with the right health care, lives can be saved.

00:01:46 Sue Saville

So for this podcast, let's find out more about the importance of access to the right treatment and care. We have three very special guests with us. We have Stela Andreea Pirvu, who is from the Association for Patients with Primary Immunodeficiencies, known as ARPID in Romania. She's the mother of a child Daniel, who received a transplant.

Also Professor Doctor Frank Staal, who's the group leader at the Department of Immunology at Leiden University Medical School in the Netherlands, currently leading projects for the clinical implementation of gene therapy for something known as RAG1-SCID. More of that and on.

And also Doctor Adli Ali, senior clinical lecturer and consultant pediatric immunologist in UKM Medical Center in Malaysia. And his work is focusing on the implementation of novel pathway targeted treatment strategies in clinical practice. Well, welcome to you all.

00:02:40 Sue Saville

So let's start with the basics that everybody living with a PID is surely entitled to receive quality treatment no matter where they live.

Professor Frank Staal, if I could start with you. What are some of the current challenges in accessing quality care? And how much do they vary across different regions and countries?

00:03:00 Frank Staal

It's very variable across the world, depending on how quickly a diagnosis is actually set and also what is available in a certain country. Some of the basic treatments include immunoglobulins and plasma products, or more advanced stem cell transplantations, or even gene therapy.

And the accessibility to those different treatments is varying, very much so. In the Western world there's a lot more available than in the developing countries. But even in the Western world, not everything is readily available because of the costs of these therapies. And also, for stem cell transplantation you need to have exactly the right donor, which can also be very difficult to find.

But it's a very important problem, as you point it out, even though these are rare diseases, collectively when you look at all the different defects, it's actually not such a rare disease. And there are many, many patients that need to have access to treatments and don't get it right now.

00:04:00 Sue Saville

And that's a good point, isn't it? Added altogether, that they're not so rare. I wonder about in Southeast Asia. Doctor Adli Ali, what's the situation like in your region?

00:04:11 Adli Ali

I guess that's a very good point that Professor Staal mentioned. And imagine this too, that Asia is the largest continent, and you know approximately about two thirds of the world population is based in Asia itself. And the problem is that Asia is so wide that several countries in Asia are still underdeveloped. And so there's a wide disparity in the accessibility they have there.

And as what Professor Staal mentioned, that you know, even in the developed country some of these treatments are still very costly. So, cost still remains a major challenge when it comes to providing these so-called universal access to all these patients.

00:04:48 Adli Ali

And as one of the things about primary immunodeficiency, because they are genetic disease, you know consanguinity is actually one of the risk factor that leads for discretion to have these primary immunodeficiencies. You can only imagine in these so-called underdeveloped or rural areas, the consanguinity rate is much higher.

Those are the patients that will be affected with these diseases. And those are the ones that do not have access. The disparity in health care is just too much, that not just they will not have access to the treatment, But even diagnosis for the so-called underlying primary immunodeficiency might not be even there until it's a bit too late. Or in fact, for some of the patients, not even diagnosed until second to the third generations of their family. So I guess other than just a cost, that might be a fact, it's about accessibility of even getting a proper diagnosis in some of these regions, which is mainly the most part of what we call Asia.

00:05:46 Adli Ali

And not just talking about country specifics too. We are just talking about in the same country, the inequality of access to this health care is quite remarkable. Because you can see, for example, in Malaysia when you talk about Kuala Lumpur, you possibly have everything you have, you know, the transplantation, the genetic analysis.

But if you just go about two to three hours away from the center of KL, there might be patients who do not have access or even doctors who are aware of their disease. So these disparities in health care is actually quite prevalent in this part of the world.

00:06:14 Sue Saville

And it be interesting to hear Stela Pirvu. You were in Romania and I understand your son Daniel appeared perfectly normal up to about four months old and then developed awful symptoms, the high fever, extensive rash, pneumonia and much more, spending many months in hospital, eventually managed to get a transplant. But for patients, in your own experience, what's it been like trying to access the right treatment and care?

00:06:38 Stela Andreea Pirvu

So in order to access the right treatment, we have to have the right diagnosis. And in his case, the early diagnosis would have come if we would have had newborn screening, because otherwise you can't detect severe immunodeficiency at birth because all children look perfectly healthy at birth and until three or four months of age they develop like any other child.

When he reached the age of four months, things started to get bad, so his health deteriorated rapidly. We ended up in the hospital for several months. We had no idea what was going on. He developed the severe infection Sepsis with multiple determinations, Klebsiella, Staphylococcus, Streptococcus and fungus. It is a miracle that he survived, I honestly have to mention that.

00:07:26 Stela Andreea Pirvu

And after several months in the hospital we discovered that something was probably wrong with his immune system. We had no idea what.

And I discovered on the internet some articles regarding a doctor who specialized in primary immunodeficiencies in Romania. But, she lived 700 kilometers away from where we used to live back then. So we took Daniel out of the hospital in Bucharest and drove 700 kilometers to the doctor in Timisoara, Doctor Mihaela Bataneant. And she immediately suspected the diagnosis of Complete DiGeorge syndrome.

00:08:02 Stela Andreea Pirvu

So in my son's case, Complete DiGeorge syndrome means that he was born without a thymus, the functional thymus. Thus he had no naive T-cells, resulting in severe immunodeficiency. Children born with athymia or no thymus, have a life span of less than two years of age, unless a corrective treatment, in our case a thymus transplantation.

00:08:24 Sue Saville

So let's just have a think about what the options have been up to now. Perhaps Adli, would you tell us what are the options and then explain a little bit more about transplantation? What options are there once some child, like Daniel has got that diagnosis?

00:08:39 Adli Ali

Yes, as you mentioned earlier, though this patient with primary immunodeficiency, you know, they have deficiency in the immune cells. So these patients tend to have the severe, persistent, unusual, recurring infections what we call as SPUR.

And the mainstay of treatment for all these primary immunodeficiencies involve preventing and treating the severe infections that the patient has, while trying to cure or trying to treat the so-called immunodeficiency that they have, or treating the underlying cost, if we may.

00:09:10 Adli Ali

So one of the thing about managing interactions is about treating infections and it is very crucial for us to actually treat this infection aggressively and rapid and fast. And this can be achieved using a potent antibiotic.

And in the case of primary immunodeficiency usually possibly require a longer course of antibiotics. And in some cases, you possibly required to be admitted in the hospital and the antibiotic to be delivered intravenous route, through the blood vessels. And of course, in some patients because of the risk of infection, they might need to continue on a long term antibiotic treatment as what we know as prophylactic antibiotic for them to prevent, you know, subsequent infections such as respiratory infections, ear infections, that might be damaging to the lungs or the ears.

And this is very crucial because in some patients with very bad or very severe what we call combining the deficiency, they might not be entitled to receive what we call the live vaccines, such as measles, mumps, rubella or the polio vaccine.

00:10:10 Adli Ali

So they are exposed or at risk of having these infections. So it is important not just for them. It's also for the family member and the surrounding to have this vaccination to prevent them from providing or actually transmitting this infection to the patient. And of course in quite a large number of patients with primary immunodeficiency, they do have the deficiency in their body to produce antibodies called the immunoglobulin.

So the way that we treat these patients is to provide what they are lacking, which is the antibodies called the immunoglobulin replacement therapy. And these can be given either through the blood

vessels, through the intravenous route or underneath the skin, what we call as a subcutaneous immunoglobulin therapy. And this is the regular replacement therapy that they usually redo either monthly or weekly dependent on delivery route.

And you mentioned Stela about transplantation, and this is just one of the field where it is so amazing and I'm very much delighted to be part of it. Because if you can see one disease where you can cure, this is one of those diseases. You know where before this, if you have like for example, what Daniel had in the case of Stela's son, you know, they're not able to survive without transplantation.

00:11:20 Adli Ali

Transplantation provides that hope, you know the cure for them. Not just you know, treating the symptoms but providing the cure. And this transplantation comes in a few ways, the one that is commonly now available in most parts of the world, is what called stem cell transplantation.

And what we do is that we put in a normal stem cells from a donor to the patient with primary immune deficiency. And we hope that through a good treatment, you know, the preconditioning what we call the chemotherapy and then the transportation works well. And if this works well and it works properly, the functional immune system can be transplanted into patients and if that happened the patient able to be cured from the treatments.

00:12:03 Adli Ali

What Daniel had, just to add on, was a thymus transplantation where they provide the thymus transplant and this will allow for the stem cell in the body of like the patient to develop normally and that is what we call a transplantation.

00:12:19 Sue Saville

Adli, that's amazing. As you say, it's rare to be able to use the word cure in medicine. We, as health journalists, we often wish to, but it's very rare. So it's fantastic. And Stela, tell us a little bit more than about Daniels experience of getting that transplant? What it's meant then? What the journey was like. And what it’s meant to him, to you, now?

00:12:38 Stela Andreea Pirvu

So in my country, primary immunodeficiency diseases patients, in general, have access to most of the regular treatments, like Doctor Adli mentioned about immunoglobulin, antibiotics and things like that. But they have very difficult access to specialized care when it comes to very rare primary immunodeficiency deficiencies.

So like gene therapy, thymus transplantation in out case, and this is due to the current Romanian legislation. These procedures are not covered by the national health insurance. And also even if the patients get to have the procedure, sometimes the lack of communication leads to very poor after transplant care. So that is why I have got very involved in patient organizations and patient advocacy after my son’s transplantation.

00:13:23 Stela Andreea Pirvu

It's important to mention that thymus transplants worldwide are only available in two centers, and that's Duke University in North Carolina in the United States and the Great Ormond Street Hospital, London, UK. So, access to care for patients with athymia is different depending on the country of origin.

00:13:43 Sue Saville

And Stela, once Daniel had had this thymus transplantation, what difference did it make?

00:13:49 Stela Andreea Pirvu

Oh, before the thymus transplantation he had no chance of survival at all. And of course because he was later diagnosed and he had a lot of pre-transplant infections and complications did arise because of that. But things got better in time, and he now he's nine years old and he has a perfectly normal life. He goes to school and he has activities outside of school as well, and enjoys childhood like any other child his age.

00:14:21 Sue Saville

That's just wonderful to hear Stela, it's absolutely lovely. And I know you've dropped off your son at school today. It's just fabulous to hear about that normal life that can be achieved after something like transplantation. But there are now even more innovative therapies coming through. Frank Staal, you're working on gene therapies. What might they offer to patients with PIDs?

00:14:42 Frank Staal

Well, gene therapy is a treatment whereby we actually use the stem cells of the patients themselves to generate a cure. Of course, those stem cells than, it's with all these very severe diseases, they are, as we just heard, genetic diseases. So, something is wrong in the genes, in the DNA. And what we're trying to do with gene therapy is correct it in the stem cells of the patient.

So we do, again, a stem cell transplantation but not with a donor, so somebody else who's healthy, but with the patient's own stem cells. And that actually, in principle works better because these stem cells from another donor, they need to be very carefully matched to the recipients, to the patient.

00:15:25 Frank Staal

If that is not the case, and that can happen, then you get a condition called Graft-versus-host disease, whereby the donor cells see their hosts, so the patient, as foreign and rejects the tissues of the patient. And that sometimes is called inverted transplantation reaction.

We used to say with kidney transplantations that the kidney can get rejected. But here it's the other way around. Here the patients get rejected by these very powerful immune cells. So that's a very difficult condition that can happen as a side effect of stem cell transplantation.

00:15:58 Frank Staal

That is, by definition, not going to happen with gene therapy. And that was actually the major reason why some 20 years ago we started to work on gene therapy for these primary immunodeficiencies and especially those where the major immune cells, the T-cells, are lacking. And so we work on a number of different conditions because that is important with gene therapy.

We talked about the importance of diagnosis, that becomes really crucial to do gene therapy. So not only do you need to know that there's a certain type of primary immunodeficiency. You also need to exactly know which gene you are dealing with, because you want to correct the right gene and not the wrong gene, then it doesn't work.

00:16:40 Frank Staal

So that becomes very critical then. But then what we can do, is take the stem cells from the patient with a crippled virus, put in the gene that is not there, and thereby in a way provide those stem cells with a copy of the correct gene.

And that then completely alleviates the problems with the development of the immune system, and a complete immune system develops them again out of the patients own stem cell. And that is now being done for a number of these diseases. It's for most of these diseases still experimental, but the field is moving very quickly.

00:17:18 Sue Saville

And very exciting to think again about the possibility for cure, but very expensive, I understand.

00:17:24 Frank Staal

Yeah, it is expensive. Stem cell transplantation, in general, is already expensive. In most Western countries it's between 100,000- 150,000 pounds/euros. So it is expensive, but the gene therapy adds quite a bit all to that. And that is because stem cell therapy is a cellular product with a certain quality. But when you do gene therapy, you really go into a medicine.

So the virus that's being used, and it sounds scary, but it isn't, it's the crippled virus that we're using as a way to put the correct gene into the stem cells of the patient. That needs to be produced under very careful conditions, and that is costly. And then the whole procedure requires many more quality controls and therefore also becomes more expensive.

00:18:13 Frank Staal

In experimental setting, that's not a problem because then it's a trial and the costs are being covered by usually a charity or a government funding organization. But once it moves into the later stages of developing a medicine, companies usually are involved, and of course companies want to make a profit. And then some of these therapies really become very, very expensive. You have to think in the range of several millions of dollars or pounds.

00:18:40 Sue Saville

Gosh, and perhaps what about some of the consensual recommendations then, in terms of improving access to treatment and care? Adli Ali, what can you tell us about those?

00:18:51 Adli Ali

Yes, when it come to this I'm highly passionate too, because you can imagine this part of the world, I mean this is the fight that we are doing for our patients, you know, for the care of families with immunodeficiency.

And with that, I think one of the fantastic things that you actually can refer to was this principle of care for primary immunodeficiency that had been jointly produced and published by IPOPI, the International Patient Organization for Primary Immunodeficiencies, together with some experts, led by Professor Helen Chapel from University of Oxford, where they actually have highlighted a few things.

00:19:25 Adli Ali

Do you know, one of the key points when it comes to this is the awareness from the stakeholders and the multiple key stakeholders on the importance of having the universal access of this, not just management, but diagnosis of this primary immunodeficiency for patients, for the ones at risk.

And in this nice principle of care, the people actually had outlined the 6 principles that every country or every region need to achieve for, for them to provide a good care for patients with primary immunodeficiencies.

00:19:57 Adli Ali

And this includes, among other things I can actually say, the need for international collaboration for scientific and clinical research. And this is the thing that actually Professor Staal mentioned, because when it comes to primary immunodeficiencies, we are talking about diseases which are in a way rare, so-called rare, if I could say it, and require a specialized treatment.

And without international collaboration, understanding about the disease, and without, you know, funding from multiple people and then the experts from different fields to come up with innovative treatments and therapy, this cannot be achieved.

00:20:32 Adli Ali

And what's really great, I'd like to introduce another thing that we just developed about two years back, what we call the IPOPI- PID Life Index. And this is an additional package as part of a continuation of the so-called Principle of Care, the one that I mentioned earlier that was published in 2014.

This PID Life Index is an interactive tool, where each of you can actually use to look at and to evaluate where are we at, or where is your country at, in terms of care that the country is providing for patient with primary immunodeficiencies. So you can actually see what is lacking and then what is required, needs to be done in that particular country or region. So that it can lead for a better advocacy, for better awareness of the so-called multiple stakeholders on what is lacking in that particular region.

00:21:19 Sue Saville

That's really helpful, Adli, thank you. Then collaboration is such a theme, isn't it? It's so important. Stela, perhaps just to summarize, I'd love to ask you if there's one thing that you could have a wish granted in terms of treatment and care, is there something that's top of your wish list?

00:21:36 Stela Andreea Pirvu

Oh, I only wish that Daniel's story and suffering was not in vain. And that the decision makers in Europe understand how inefficient and dangerous and costly operation, diagnosis are these days without proper tools like newborn screening, in our case would have made a huge difference.

And I know that there are so many health issues that need to be addressed, and diseases are never a priority in many countries. But I believe that it is against human rights to have the cure for a disease and to have the possibility to access that curing in time, and to simply ignore it and leave the patient to suffer and ultimately die.

00:22:14 Sue Saville

That's a great point to end on their Stela. Thank you so much to all our guests today, to Stela Pirvu, to Doctor Adli Ali and Professor Frank Staal. Thank you so much for all those insights into treatment and care options and what's coming up on the horizon.

And yes, of course, it's so important to remember that access to health care is a basic human right and that every PID patient is entitled to that correct diagnosis, treatment and care. And with access to those, lives can be saved. So thank you all very much indeed. It's been great talking to you.

00:22:44 Adli Ali

Yep, thank you so much. It's great to talk to you and to have Professor Frank Staal and Stela together.

00:22:49 Frank Staal

Yeah, my pleasure as well. I really enjoyed it tremendously. And like you indicate, it's very important to raise awareness for this very complex disease.

00:22:58 Stela Andreea Pirvu

Thank you so much for inviting me and I agree with Professor Staal that this is very important and raising awareness is very important in order to have access to treatment and cure.

00:23:08 Sue Saville

Thank you all very much indeed. And until next time, everyone listening can help promote this campaign using the hashtag WPIW talks. So, for me, goodbye for now.