Podcast Transcript:
Short stature conditions including SPIGFD: Patient Cases

Brought to you by:
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Dr Andrew Dauber
Welcome to the podcast. The title of today's podcast is short stature conditions, including severe primary IGF-1 deficiency, a patient case discussion.

My name is Dr Andrew Dauber and I am the Chief of Endocrinology at Children's National Hospital in Washington, DC. Today we're going to focus on some patient cases in real clinical practice, focusing on the area of severe primary IGF-1 deficiency.

I know many of you are probably very familiar with evaluating patients for short stature, especially seeing patients with growth hormone deficiency who may present with a low IGF-1 level. We're not going to really discuss the workup of patients with growth hormone deficiency today, but rather we're going to focus on other patients where the IGF-1 levels are low, but the growth hormone levels are actually high. And this might point you to a case of primary IGF-1 deficiency.

Now I'm going to introduce you to my co-host today, Dr Marta Ramón, joining me from Barcelona. Marta, could you please introduce yourself and tell us all a little bit about why you think this is an important topic.

Dr Marta Ramón Krauel
I'm Marta Ramón and I'm the Chief of the division of Pediatric Endocrinology at Hospital Sant Joan de Déu in Barcelona, Spain. And today, we're very happy to present this podcast, which we're going to do in a practical manner with clinical cases, discussing about severe primary IGF-1 deficiency, which is a rare condition that as pediatric endocrinologists, we might not see very often. But it's important that in our practice we are able to make the appropriate diagnosis. Sometimes it's going to be more clear cases, sometimes it's going to be not so severe cases, and that will take us, will be a challenge for us to diagnose, but it will be very important for us to make the correct and early diagnosis in order to treat appropriately and have the appropriate management for these patients.

Dr Andrew Dauber
And I just want to draw everyone's attention to the fact that we have two other podcasts in the series. The first one is about short stature in general, key challenges in diagnosis and management. And the second one is about severe primary IGF-1 deficiency, really focused on the diagnosis and management.

Well, today we're going to focus more on clinical cases. Now, I know that the names and abbreviations can be a little confusing. So just to help clarify that, some people refer to this as primary IGF-1 deficiency, some people add on the severe, and it becomes SPIGFD. This can also be referred to as growth hormone insensitivity or growth hormone resistance. And a specific classical type of that is something called Laron syndrome.

So now, I know, Marta, that you had, recently you had a patient with a classic presentation. I'd love to hear more about that patient's case and then we can discuss the diagnosis and management.

Dr Marta Ramón Krauel
Let me tell you about this case. This is the case, as you say, of, the form of severe primary IGF-1 deficiency. And so this is a girl. When she presented to the clinic, she was only two and a half years old, and she presented with very severe short stature.

When doing the history with the parents, she was born at 38 weeks, was almost 3kg and 48cm at birth. So pretty normal. Not SGA [small for gestational age] or anything. And then she was achieving normal milestones for age, and she was doing well, but she was definitely growing very poorly since a few months of life. And then, other than that, they refer that she had these episodes every once in a while that were quite often lately, that she presented with, she was sweaty and pale. And when they give her a bottle or some food, then they kind of regress. So pediatrician thought it was likely hypoglycemia.

In terms of the family history, so the parents' height is pretty normal. However, when asking more about the family, the maternal grandfather had a very severe short stature. So did the sister of this grandfather. So, then we talk a little bit more about the family history and there was history of consanguinity among both families.

On physical exam, this little girl, at the age of two and a half, she was 66cm. So that -7.2 standard deviation. So when we're talking about severe short stature we're talking below 3

standard deviation. So this girl was 7.2. So really, really very short. In terms of the physical exam, it was very obvious when I saw her that she was having one of these episodes of paleness and sweating. I did take a blood sugar, just in clinic that day, and it was low, it was 38. So other than that on the physical exam, the appearance was, the face she had, midface hypoplasia with the nasal bridge being like flattened and with frontal bossing. Other than that the body proportions were pretty normal and she had, the hands and feet were quite small. Other than that she looked well-nourished and pretty normal.

With this, obviously very severe short stature so we did all the normal laboratory tests that we all in Pediatric Endocrinology do. And she didn't have any other systemic illnesses. And with the blood test it also came back normal CBC, normal chemistry, no celiac disease, normal thyroid function. But definitely the IGF-1 levels on this blood test were undetectable and the BP-3 levels were low. With that we perform growth hormone stimulation test. It came back with stimulation with glucagon. And with that the peak of the growth hormone was 28. And it was very apparent that at baseline before the growth stimulation, the growth hormone levels were around 20.

At this point we have a girl with very severe short stature that started very early in life, with hypoglycemia, consanguinity in the family, undetectable IGF-1 levels, but different from growth hormone deficiency. Growth hormone levels were high, which was not what we expected. So anyway, this is a little bit about severe primary IGF-1 deficiency, right?

Dr Andrew Dauber
Your patient really had many of the classic features as you outlined. And to highlight, as you said, the severity of the short stature is usually much more severe than you would see with growth hormone deficiency. Obviously those biochemical features are very classic for a form of growth hormone resistance, right?

Where you would expect, with low IGF-1 levels, you might suppose, oh, the growth hormone levels are going to be low like in severe growth hormone deficiency. But here that high growth hormone level even before stimulation is highly suggestive of a form of growth hormone resistance. And I also want to highlight something that you said is that you looked at other causes, other chronic illnesses, whether they could be leading to a secondary IGF deficiency. Could she have had liver failure or some other inflammatory disease? But no, she otherwise was healthy. Pointing to the fact that this was severe primary IGF-1 deficiency. Right? This was a problem due to growth hormone resistance, you know, with those classic features. She had this spontaneous hypoglycemia, the mid-face hypoplasia, the frontal bossing. Sometimes these patients have high pitched voice, often. And if they're boys, they can have underdeveloped genitalia as well. So many of the really classic features that your patient had. And you also pointed out that this is a recessive disorder, in its classical form. I would guess at some point this patient probably had some genetic testing done. Was that the case?

Dr Marta Ramón Krauel
That is the case. And yes, she had bi-allelic, so two mutations of the same mutation at the level of the growth hormone receptor, like loss of function mutations, meaning that this is what we expected, right? This is a severe form with hypoglycemia and mid-face hypoplasia.

So we're more thinking about the classic Laron and then the genetic mutation of having the two copies or biallelic, of the same mutation pointed to that she had Laron syndrome and actually makes sense. This is a consanguineous family so when we did segregation studies, the father and the mother were carriers of that same mutation.

And then interestingly, I had pictures of the grandfather. The grandfather never had hypoglycemia, but he definitely had also the mid-face hypoplasia. And then we did genetic testing on him. And obviously he had the same two mutations as our patients. So it was pretty interesting.

Dr Andrew Dauber
In a family that's consanguineous, especially over multiple generations, sometimes the pattern of inheritance can be confusing because, you know, you can have a recessive disorder that shows up in multiple different generations due to the inbreeding relationships. But this is classic to have bi-allelic recessive mutations in the growth hormone receptor as the primary cause of Laron syndrome, which is a form of severe primary IGF-1 deficiency. Great. So you've made the diagnosis. You have the patient there. How did you treat this patient? You know, what was your indication for treatment and how did you go ahead and treat them?

Dr Marta Ramón Krauel
As you know, these patients, they do not respond well to growth hormone, especially when they this bi-allelic mutation. There is definitely a huge resistance to growth hormone. And actually growth hormone levels were already high at baseline. They were already 20. And even, I forgot to mention, but we did growth hormone stimulation tests just because the genetic testing will take longer and we wanted to define the patient better. And after giving growth hormone, a dose of 0.04 milligrams per kilo per day during four days, the IGF levels remain undetectable.

Dr Andrew Dauber
So that, you're saying that's an IGF-1 generation test, right?

Dr Marta Ramón Krauel
Yes.

Dr Andrew Dauber
So people use that clinically, as you're suggesting. Where you give a test, basically a test dose of a high dose of growth hormone for a few days, and you want to see the IGF-1 increase in growth hormone deficiency, but in growth hormone resistance it can't increase. And I'll say, just for those listeners out there, sometimes if you don't have access to genetic testing or you're unsure about the diagnosis, somebody who's not responding to growth hormone treatment and their IGF-1's not coming up. You really should question, wait, did I get the right diagnosis or could this be primary IGF deficiency? Anyway, back to you Marta.

Dr Marta Ramón Krauel
That helped us because the genetic testing took a lot longer. So with that we had it clear that there was a severe primary IGF-1 deficiency. And so we decided to start treatment with

recombinant IGF-1 because that's what would be the treatment of choice in this case, however, you know what, one of the concerns is that when you start the patients can have hypoglycemia, especially these Larons patients. And this girl already had a lot of hypoglycemia events. So, before we did that we had to re-educate completely the family in terms of their feedings and the schedule, they also had to know about how to take measurements of the blood sugar and what to do when there was a hypoglycemia.

Once all this was in control, then we started with recombinant IGF-1. So we started, at the lower dose, 40 micrograms per kilo, every 12 hours. And then, as she was tolerating it, we increased to 80 micrograms per kg and then to 120 micrograms per kg, which is the recommended dose. And we did this escalation in order to be able to make sure that she was tolerating it well. And we were giving this in accordance to the feed. So we make sure that the effect of the recombinant IGF-1 wasn't in the times where she was fasting and so try to accommodate as much as possible her schedule.

Dr Andrew Dauber
I think that's a really important point. I've seen some people get confused about the dosing. So the dosing is twice a day of subcutaneous injection. And as Marta said, you start out with 40 micrograms per kilogram per dose. And usually people escalate every week or two, up to the 120 micrograms per kilogram per dose twice a day, which is the maximum dose. But the hypoglycemia really is the limiting factor. So you've got to make sure to counsel patients to eat something with their dose to monitor the blood sugars after the dosing to make sure that they're not having significant hypoglycemia, and really make sure they have that nutritional support and know how to monitor for signs and symptoms of hypoglycemia. Excellent. So how did your patient respond to treatment?

Dr Marta Ramón Krauel
She responded well. During the first year she increased her height SDS by 0.6 and then by the following year by 0.4 more. So went up to 1 standard deviation and little by little, but growth velocity in the first year it was almost 9cm per year. Although you have to take into account that she was only two and a half at the time. So the growth velocity is a little bit different than if you are a little bit taller. So in general, effectiveness is better in these patients, in Laron syndrome patients. So the classic Laron syndrome patients are the ones within the severe primary IGF-1 deficiency group that actually respond better on gaining standard deviation yearly. And that's what the data, as you know, there's a registry that, it's a study where we introduce all the patients with recombinant IGF-1 and so we can gather data about real-world evidence about what's going on. Although we need to know what's going on in final adult height and this is it's probably going to take a long time to know what's going on.

Dr Andrew Dauber
I think that's very true that these registry data is really important for us to learn what's happening long term. And I think a few important points, like you pointed out, was that in these patients the growth velocity can increase significantly. But not as much as you see in patients with severe growth hormone deficiency treated with growth hormone. Because growth hormone has affects through IGF-1 as well as independent of IGF-1. So there have been published trials that show the first-year response and second-year response, which

you can look up. But, this is the treatment of choice for patients with growth hormone insensitivity / severe primary IGF deficiency. And Marta, as you were saying, in the registries there are patients with documented genetic mutations causing the Laron syndrome. But then there are other genetic causes or under, you know, undiagnosed causes of severe primary IGF-1 deficiency and that is a clinical description in the FDA approval for recombinant IGF-1, is when you have both a height and an IGF-1 below minus three standard deviations. I'm not sure, is that different in Europe?

Dr Marta Ramón Krauel
You have to have severe primary IGF-1 deficiency and your stature should be below three standard deviations of height. And then the IGF-1 levels, I think that's what changes between the United States of America, which is ≤-3 standard deviation, and for Europe, it's <-2.5 percentile.

Dr Andrew Dauber
So a little bit different. And what other side effects were you looking out for? We talked a lot about the hyperglycemia but what are the other side effects with recombinant IGF-1 therapy?

Dr Marta Ramón Krauel
Well definitely anything that is subcutaneous you have to look at the injection site reactions, which could be often. Also IGF-1, because it promotes growth, you know, IGF-1 promotes growth so you better look at the tonsils sometimes in the exam. And I will say like the more worrisome, and that's why we are very interested in the registries long-term, it's because, as you know, IGF-1 promotes growth and our concern is that it could promote now growth of malignancies. And so we really need to keep following on that and especially to know, I think for physicians at this moment with this drug, it's important that we use it under the circumstances that they have a diagnosis of severe primary IGF-1 deficiency. Because, as you pointed out, it's very important that it's not a secondary cause of IGF-1 deficiency.

Dr Andrew Dauber
I think that's such a good point. Given these concerns about potential malignancy risk. Really you want to make sure you're following the label and that you've diagnosed patients correctly. Great. Well that was a wonderful presentation of a patient with the classical form of severe primary IGF-1 deficiency. Thank you.

Dr Marta Ramón Krauel
Those are easier but I know that sometimes we have milder cases. Well, Andrew, so not all the patients are so obvious. So I heard that you have been managing other patients which could be a little bit more challenging today

Dr Andrew Dauber
I had a really interesting patient who I'll just tell you briefly about. He initially presented at age 4 with a height just below -3 standard deviations. He continued to, kind of, parallel the curve, wasn't catching up and at age 8 still had a height below -3 standard deviations, and he didn't really have the classic findings. So his IGF-1 was just at the lower limit of normal but also had a growth hormone stimulation test done and was found to not be growth

hormone deficient. And he had a father also who had a height around -3 standard deviation. So this was more looking like a dominantly inherited form. It was not a consanguineous family, there wasn't other family members. And interestingly, he had a big sequencing panel done and he was found to have a heterozygous mutation in the growth hormone receptor. So just one copy wasn't working well, but his mutation was very unique in that it was right at the portion of the growth hormone receptor where it anchors into the membrane. And what it did was it resulted in very high levels of growth hormone binding protein. So growth hormone binding protein is a protein that helps carry growth hormones through circulation. And it's made up from the extracellular component of the growth hormone receptor.

His mutation was very unique in that it was causing these high levels of the binding protein. And the binding protein was actually acting as a sponge, sucking up all the growth hormone, preventing it from binding to his receptor. So this was a milder form of a growth hormone resistance and insensitivity. And actually, we decided to try and overwhelm this form of growth hormone resistance with very high doses of growth hormone, very, very high doses. And we were able, with that approach to make the IGF-1 come back into the normal range. And he's grown much better.

This is a very unique patient, a single-patient study. People can read more about it if they want in the published article (Merchant et al, 2024). But just to show you that there can be a spectrum of growth hormone resistance from really the severe primary IGF-1 deficiency in its classical form of Laron syndrome, there can be milder mutations in the same receptor. And, you know, why don't we briefly mention there can be other mutations in the signalling pathway. You know, which can also lead to forms of growth hormone resistance.
So Marta, I think you've seen patients with ALS deficiency. You want to tell us briefly about that?

Dr Marta Ramón Krauel
Yes, so patients with ALS deficiency that had short stature but not so severe and low IGF-1 and very low BP-3 levels and usually we measure ALS but when we end up measuring that it was low. But this patient, they are not so severe. But the point is that, if you see a patient that is not growing well, despite it's not so severe as case 1 and we see very low IGF-1 levels and if they have also low BP-3 levels that maybe if your growth hormone is working well, we should start thinking about severe primary IGF-1 deficiency, and you have seen other cases, right Andrew?

Dr Andrew Dauber
And just to clarify, for all of our listeners, ALS is the acid-labile subunit. It's a binding protein that helps stabilise IGF in circulation. So you have the low IGF-1 and BP-3 levels, but again a milder form of growth hormone resistance. I've seen patients also with STAT5b deficiency. So STAT5b is a transcription factor downstream of growth hormone receptor that actually leads to the transcription of IGF-1. And those patients also have severe primary IGF-1 deficiency. They also have significant immunodeficiencies and autoimmune disorders. So they have a more complicated phenotype. But again, just like you were saying, if they're making growth hormone but the IGF-1's low, we should start thinking of other causes.
So, excellent. We talked about some of the differences. Marta, any key points that you want to make sure we highlight about severe primary IGF-1 deficiency before we close?

Dr Marta Ramón Krauel
We pointed out everything. But I think it's important that at least there is awareness. And so low IGF-1 with no other secondary cause, low BP-3, normal growth hormone, we should definitely think about severe primary IGF-1 deficiency. And then if we can know more, the more pathophysiology we know the better we'll be at diagnosing early. But also, I'd like to start getting better treatments and more targeted treatments. I think that's the future of endocrinology. There's still a lot of rare forms of short stature that we should be, doing something better.

Dr Andrew Dauber
I totally agree. And I think what's so important with identifying this disorder is that growth hormone treatment will not work, as you said, this is not growth hormone deficiency, right? There's sufficient growth hormone and resistance to growth hormone. So making this diagnosis early, starting on appropriate therapy with recombinant IGF-1 early can really have a tremendous impact on these patients' long-term growth and health. So I think with that, I'm just going to thank our audience for listening and draw your attention again to the other podcasts in the series. If you want to learn more about these topics, and thank you again. We hope you enjoyed the podcast.

Tonke de Jong (COR2ED)
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