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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Neonatal Diabetes: A Special Case of Type 1 Diabetes

Each month ReachMD XM160 presents a special series. This month is Focus on Diabetes. Listen each hour at this time, as we explore with America's top medical thought leaders for latest information on diabetes.

You are listening ReachMD, The Channel for Medical Professionals and I would like to welcome you to a special series today "The Focus On Diabetes." I am Dr. Dan Patracek, your host and with me today are two special guests, I have Dr. Louis Philipson of the University of Chicago. Dr. Philipson is the Professor of Medicine and is also the Director of the University of Chicago Comprehensive Diabetes Center.

DR. DAN PATRACEK:

Welcome Dr. Philipson.

DR. LOUIS PHILIPSON:

Thank you, nice to be here.

DR. DAN PATRACEK:

The topic today is, I guess the simplest way to put it is, Neonatal Diabetes, which is at least has been believed for a long time to be a special case of type 1 diabetes, and I thought may be we would begin with you Dr. Philipson, may be you could tell us a little bit on, you know, general background on type 1 diabetes and what was the thinking, let's say, several years ago before some of these new findings.

DR. LOUIS PHILIPSON:

Sure, well in general type 1 diabetes is thought to be of an autoimmune etiology, so they are considered to be a T-cell defect, so the white blood cell of the T cell family for, I would say to this day, unknown reasons attack the insulin-secreting cells and then sort of a lot of stuff rolls out from there, but for a long time, pediatric endocrinologist realized that the diabetes that happens before the age of say 6 months at presentation, 6 months of age, is really a different sort of thing for a lot of different reasons. Recent research has shown that the kids who have diabetes at that early age have the low risk or normal-risk HLA antigen, so that means that their immune system is not the ones that are associated with autoimmune phenomenon in general and there is some other features of that early onset disease that seemed to be pretty different, although these young children do present in ketoacidosis. So, it always had this different name of neonatal diabetes.

DR. DAN PATRACEK:

So, tell us may be just a little more specifically in the clinical presentation of neonatal diabetes, what were the features that are distinct, let's say, from what we think of this type 1 diabetes?

DR. LOUIS PHILIPSON:

Well, the etiology can be similar. So, it's easier in some ways to see the similarities. You can have kids present in diabetic ketoacidosis within the first few days of life up until say about 6 months or so, but what is clear is that they don't have the antibodies for the most part, now there are some rare exceptions, but when I say antibodies, it has become state-of-the-art to test for several antibodies. The most important and generally useful being the anti-GAD65. This is an antibody against glutamic acid dehydrogenase, which has become the most useful indicator of autoimmune disease and the autoimmune diabetes and these kids are negative.

DR. DAN PATRACEK:

So, for example the C-peptide level in these children is also absent. Is that so?

DR. LOUIS PHILIPSON:

For the most part that's true. I mean what they can have are may be early on detectable C-peptide, but by the time they get diabetic ketoacidosis and soon after that, they are also C-peptide negative and that can be like autoimmune diabetes too, although some of the more current sources say, that like Dave Harland of the NIH, that up to 10% or 15% of his type 1 autoimmune patients are still C-peptide positive even some years out.

DR. DAN PATRACEK:

May be you could give us just putting us inside your head, what were the initial clues that this disease was really going to be different, let's say from the clinical point of view and then may be you could tell us from the scientific and fundamental research point of view?

DR. LOUIS PHILIPSON:

Well, we have to really point to the work of Andrew Hattersley, at Exeter in the UK, which has been called Peninsula Medical School, that Andrew's team was really ahead of the game in sorting out that a particular ion channel mutation was at the heart of over half of all of these neonatal diabetes cases. So, why that was interesting was because of the lack of autoimmunity and because in at least some families, there was a very strong inheritance, in some cases dominant, that a genetic search for the specific mutations that could cause neonatal diabetes as opposed to an autoimmune cause was begun really around 2002-2003 and in part that was because of the excellent registry that was available in the UK and other countries in Europe for kids with very early-onset diabetes. So, that early thinking led to a series of genes that were candidates and one of them became this channel in the case of say, of Lilly Laurie's daughter, with this particular channel, which is the target for sulfonylurea drugs. The channel is called the KTP channel, has 2 subunits and mutations in those subunits were found to prevent the insulin-secreting cells from secreting insulin. So, that was the background scientifically and then around 2004, the Hattersley Group showed that sulfonylureas, in fact, could block the channel and cause insulin secretion in some of these patient's with neonatal diabetes and furthermore in that year 1 patient could be transferred off of insulin. Unfortunately, this had the equivalent of sort of one hand clapping if you will. I mean that there was very little notification and it was only until Andrew's Group was here in Chicago and let us know about a paper they have been preparing to be published in New England Journal where now they had over 50 cases where they had identified mutations in the gene called KCNJ11, one of the two critical subunits of this channel, as a cause of the neonatal diabetes and that's is when I also met the <_____>.

DR. DAN PATRACEK:

That's fascinating. Let me just kind of side track just for a moment, the fact that the sulfonylurea drugs seemed to rescue this type of diabetes and act on, at least in this particular case on the specific

potassium channel you described makes one wonder about the type 2 diabetics. Is that the type of therapy working in the same way?

DR. LOUIS PHILIPSON:

Well, it exactly is how that therapy works. So, the sulfonylurea drugs have been shown since about the 1970s to cause insulin secretion in someone with beta cells or with type 2 diabetic, by blocking this channel and when the channel is blocked, there is sort of Rougoldberg kind of set of consequences. Potassium accumulates in the insulin-secreting cell, that causes the cell to depolarize. So, now we think about insulin-secreting cells as if they were neurons or cardiac cells that fire. So, these are electrically activated cells. So, when the cell depolarizes, you have a series of events that allow calcium to get into this cell and then another series of miracles happen and then you get insulin secretion. So, in fact, it's exactly how sulfonylureas work by targeting this potassium channel, which otherwise in normal physiology would be closed just by glucose metabolism.

DR. DAN PATRACEK:

So the distinction between the type 2 diabetics in this one is that in type 2 diabetics, there probably is an existing normal secretion of insulin and now we are just asking the system to secrete more.

DR. LOUIS PHILIPSON:

In terms of the drugs in type 2 diabetes, yes. So, I describe it as sort of whipping the beta cell and of course when I was, I mean just a few years ago, sulfonylureas were about all we had to treat type 2 diabetes. Now, I would say because of the concern that sulfonylureas eventually stop working in type 2 diabetes where insulin resistance is also a problem, sulfonylureas have dropped to maybe a third-line drug in type 2. When we are talking about neonatal diabetes, sulfonylureas do not seem to lose efficacy over time and there is a couple of patients that the Hattersley Group have uncovered in Europe, who have inadvertently been treated with sulfonylureas for 40 or 50 or more years and they still continue to work on people with these channel mutations.

DR. DAN PATRACEK:

What was the situation once it was discovered that there is a possibility for rescuing some of these children? What took place next?

DR. LOUIS PHILIPSON:

As I said, we were able to hear about the series of patients, which was the largest series in the world to date in, I would say, May or so of 2006 and what excited at least me, I guess, the possibility that we ought to be looking for these people very actively, so people with neonatal diabetes, who could then have genetic testing to see whether their mutation was in principle treatable by oral agents and not by insulin. So, the two things to keep in mind is that these in permanent neonatal diabetes, it is indistinguishable from type 1 diabetes clinically and the second point is that most physicians are not in a position to make a diagnosis without thinking about it and of course it is very rare. So, those 3 things come together. So, the rarity is very, very important to stress at this point in the conversation because neonatal diabetes itself of all causes and this channel mutation is only one of several causes of neonatal diabetes. It's about 1 in a 1000 of all cases of type 1 diabetes, so very rare and when it comes to the incidence in terms of the number of livebirths, it's about the estimation is between 1 in 200,000 and 1 in 400,000 livebirths. So, by comparison, it makes cystic fibrosis look like a common disease.

DR. DAN PATRACEK:

I did read in one of the articles that there was an estimate of the percentage of neonatal diabetics that had some sort of, that had a particular or specific mutation, I think, it was the KATP that channel mutation. Is that correct? Is it they are a high percentage, or?

DR. LOUIS PHILIPSON:

It's very high. So, almost half of them have a KATP channel mutation of which about, 80% to 90% of those are mutations in the KCNJ-11 gene and the rest are in the ABCC-8 gene, which is the other protein that makes up the channel. The amazing thing is that most of those are responsive to sulfonylureas.

DR. DAN PATRACEK:

So, may be you could have described briefly the results of the first clinical trial.

DR. LOUIS PHILIPSON:

The results are astounding and our work certainly backs that up and there have been numerous followup papers from different groups across the world. The amazing thing is that giving sulfonylurea drugs to people with the channel mutation form of neonatal diabetes results in an improvement in A1c, typically you know someone might be in the 9% range as a child, then the A1c has become very close to normal into the 6+ range, 6% range, and while that's happening, the incidence of hypoglycemia has reduced dramatically and in some cases it does not happen at all. So, you have sort of this quadruple benefit of no injections, decreased swings, almost minimal hypoglycemia if any, and a dramatic improvement of A1c. So that is, I mean, you just cannot beat that.

DR. DAN PATRACEK:

That must be such a miraculous experience for families and physicians taking care of the patient. I would like to thank Dr. Louis Philipson of the University of Chicago School of Medicine, and we have been discussing neonatal diabetes.

I am Dr. Dan Patracek and you have been listening to a special series Focus on Diabetes on ReachMD, The Channel for Medical Professionals.

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