Understanding Lecithin Cholesterol Acyltransferase (LCAT) Deficiency Disorders

Lecithin cholesterol acyltransferase (LCAT) deficiency is a genetic disorder that affects the body's ability to process cholesterol. It is characterized by cloudiness of the clear front surface of the eye (corneal opacities), a shortage of red blood cells (hemolytic anemia), and kidney failure. Familial LCAT deficiency is one of two types of LCAT deficiency; the other type of LCAT deficiency is fish-eye disease. Both types of LCAT deficiency are caused by genetic changes in the LCAT gene and are inherited in an autosomal recessive manner.

Fewer than 1000 people in the US have this disease and we are talking to Dr. Marina Cuchel from University of Pennsylvania to understand the condition better. We will be touching upon various aspects of the disease not limited to symptoms, diagnosis, treatment and management.

Full Transcript:

Priya Menon: Hello and welcome to CureTalks. This is Priya Menon, your host. Today on CureTalks, we are discussing a very rare disorder, namely the Lecithin Cholesterol Acyltransferase deficiency disorders or the LCAT deficiency disorders. We have with us Professor of Medicine. Dr. Marina Cuchel from the University of Pennsylvania. Dr. Cuchel's research focuses on novel therapeutic strategies for the treatment of rare genetic disorders of lipid metabolism. Joining. Dr. Cuchel on the panel are advocates Jason Marshall who lives with LCAT deficiency disorders and Beverly Ridings who was a caregiver to Jason. Welcome to CureTalks everyone.

Jason Marshall: Thank you.

Dr. Marina Cuchel: Thank you for hosting us, Priya.

Priya Menon: Lecithin Cholesterol Acyltransferase deficiency disorders or the LCAT deficiency disorders is a very very rare condition with less than 125 known cases the world over. Dr. Cuchel, to start with let's understand what this condition is all about. Can you explain in layman's terms what LCAT deficiency disorders is, which part of the body is affected and what causes it?

Dr. Marina Cuchel: Priya, thank you very much for giving us this opportunity. I really hope that through this conversation we can really increase the awareness of this as you said very rare condition, so the medical term for this very rare disease is ultra rare disease. So, we are talking about ultra rare disease. So what it is LCAT deficiency is caused by the complete or partial absence of this protein that as you said is called Lecithin Cholesterol Acyltransferase or LCAT for short and due to a mutation in the gene that contains the information for the cells to produce LCAT. And so what happens when LCAT is now present, LCAT is

produced by the liver and is secreted in circulation and has a very very important function in circulation and that is that of tracking cholesterol inside some complex molecules that are called lipoprotein that trapping the cholesterol are able to take it back to the liver to be eliminated. And you can think as oil and water do not mix together and cholesterol and triglyceride are fats that like oil that cannot mix well in the bloodstream, so they need this complex particle lipoprotein to circulate and be safely deposited in the liver where they need to, they can't be excreted and processed to be eliminated. So, when LCAT is absent, the cholesterol cannot be trapped and so it gets deposited somewhere in the body and there are two organs that are preferentially targeted and creating damage, potentially creating damage. And so, all patients, all people that have LCAT deficiency have two characteristic features, one is that they have very very very low level of a lipoprotein that is called HDL and in particular the cholesterol that is carried by this HDL. So, they have very low level of HDL cholesterol and the other characteristics that every patient has is what is called corneal opacity, that is practically a clouding of the cornea that is the most external part of our eye and so this patient have a bluish greyish hue shade on their eye. So these and maybe an increased risk of heart disease is what the people that have the milder form of LCAT deficiency that is called Fish Eye Disease because of the characteristic of the eye or FED for short may have. But it is also a more severe form of LCAT deficiency, it's called Familial LCAT deficiency or FLD that has two other silent symptoms that can occur. One is the anaemia because too much cholesterol is deposited in the membrane of the white blood cells and make them very easy to break and so there is anaemia. And the other organ that is terribly affected is the kidney because the excess of cholesterol goes and get deposited in the kidney and is toxic for the cells of the kidney that then die and so there is a renal kidney disease as a consequence. So, this is what LCAT is and what are the cause of this condition.

Priya Menon: So, Dr. Cuchel you said some of lower levels of HDL and opacities in the eye, are these the signs and symptoms or is this much progressed version of the disease. Like I'm just trying to understand like if I want to get tested, what is it that I should be looking for? What should be that indicator which tells me yes, I should get tested?

Dr. Marina Cuchel: Priya, thank you very much for asking this question. This is really important. It is very important because these conditions usually diagnosed too late when some people for example with FLD noticed that their ankle gets swollen because of the kidney disease and so many time the few patients that we know of many times they are diagnosed because they already have the manifestation of the disease and until that moment the disease was silent. So how we recognize we need to be better at recognizing this condition, both the patients need to be more advocate of themselves and the doctors of these patient need to learn how to recognize the disease. And so the first thing that I say to you, the first sign that usually appear is this corneal opacity, this cloudiness on the eye that usually become apparent during the early teenage year and unfortunately because they do not create big problem to see, of the vision they frequently are not investigated, this appearance of this strange hue in the eyes is usually not investigated further or if it is investigated is told to be something else maybe a signal argos that is frequent in people with very very high cholesterol level or in the older patient. The other bell that should ring in our head is if you do a lipid panel if you look and have the doctor that prescribed to you a blood test to check your cholesterol, you will notice that your HDL are very very low and unfortunately, although many guidelines say that a lipid screening, a blood test for lipids should be done in school age years and young adult, is rarely done. And so many time this is discovered because someone in the family has a heart attack or have renal disease or something that prompted the doctor to say okay, let's see if other members of your family have these. And so, during this screening that is called opportunistic screening you may discover that one family member also has very low HDL level and in that case follow-up should be done to try to discover why these patients have low HDL. And so, a clinical confirmation of the presence of the LCAT deficiency is to test that in the blood how much activity the LCAT has, how much LCAT activity is present in the blood of the person that you want to test. This however is a very very specialty test, only few labs in the whole world are doing it. And so, it is easier if available doing a genetic testing for all and tested for all the cause, the genetic cause of low HDL

including LCAT and so you can diagnose LCAT deficiency through that. If neither of the two tests are available, usually you arrive at the diagnosis putting together all the pieces of this patient, the lower HDL, the renal biopsy, if the person has renal disease, the anemia, the corneal opacity and you make the diagnosis of the LCAT deficiency.

Priya Menon: Thanks, Dr. Cuchel. Beverly, we would like to really hear from you. I've heard from Dr. Cuchel how you advocated for getting Jason tested and I think it'd be really great to hear your side of the story how it unfolded, can you please share that with us?

Beverly Ridings: Well, my husband passed away, our primary care physician said he died pretty early, pretty massive heart attack, maybe you need to have the kids tested to see if there's anything going on with them. So that prompted us going to a major medical center and beginning with whole process of being tested and it was a few years before a good name was given to the disease. We went to a series of a lot of blood tests and Jason was quite young and we did skin biopsies and cloning of skin cells and all sorts of like I said blood test before it really came out what exactly is the name of this disease. In the meanwhile, we realized that he has very high cholesterol, very high triglycerides, so we worked on dietary management, which is really hard to do for a young child. I could be in control of some of that but not all the time and while dietary management is really important you can't fight genetics very well. If it's already there in the genes you just got to have to roll with it and make the best habits that you can diet, exercise, regular physicians visits and blood tests.

Priya Menon: Jason, what is your side of the story, I know you were diagnosed even before your symptoms appeared, right? How has your condition evolved over the years?

Jason Marshall: Well initially, of course we observed the extraordinarily low HDL levels, and I believed in my teenage years the corneal opacity began to show up but the corneal opacity even today is progressed has had no effect on my vision. Symptomatically I really didn't have any symptoms until about age 29 when I started to go into end stage renal failure and that was the first time that I actually myself really took the disease seriously. I'm little ashamed to admit that in my younger years I was very dismissive of it because I was anti symptomatic and the young and dumb side of that equation too, mom said young, I add to that uncooperative. So, at about age 29 when I was in the end stage renal disease became very physically symptomatic and we started looking at doing a kidney transplant and that's when it finally clicked for me that I needed to become more proactive in my healthcare overall and not be dismissive of this disease.

Priya Menon: So, you have undergone kidney transplant twice, is that right?

Jason Marshall: Yes.

Priya Menon: Yes, and also a liver transplant. Would you like to share that with us as well?

Jason Marshall: Absolutely. We did the first kidney transplant in 2011. My wife was a match for me. She gave me one of her kidneys. The thinking at that time we were working with Dr. Miller at University of Maryland, he is now working with Dr. Cuchel at University of Pennsylvania. The thinking was that there was possibly, is no know therapy, no existing therapy for this disease aside from treating symptoms that potentially if we did a liver transplant, partial liver transplant, may be the healthy portion of the liver would be able to produce a healthy LCAT enzyme, so we opted to proceed with that and coincidently and miraculously my wife was also a very good candidate for a liver transplant. In fact the surgeons at time of transplant were throwing numbers, statistics of 1 in a billion match from both kidney perspective and then they would be able to do the liver as a living donor. So, we gave that a try which showed some initial success, we did a small lobe transplant and immediately following the transplant we had some better HDL numbers, normally my HDL is less than five, within immediately in the hours following the transplant, I was as high as 17 but within a few days that fell off to back to my normal range, unfortunately. So it is the form of therapy it was not successful and we're still not sure why some of the theories include the possibility that I may have developed antibodies to the LCAT and to my knowledge we still haven't successfully tested that theory. So that's the story of the liver transplant and my transplanted kidney lasted almost 10 years. I have a particularly High sensitivity to tacrolimus, one of the key anti-rejection medications, so that caused a lot of damage to my kidney and it's not known whether or not that particularly high sensitivity is associated with the FLD or if it's just unique to me, but that ultimately that in combination with the continue progression of my disease continue to do damage to the transplanted kidney. So, in 2021, we did a second kidney transplant. In 2020. I was in stage renal disease and we did a second transplant in 2021. My sister-in-law was kind enough to give me one of her kidneys so I'm burning through my family spare parts pretty quick.

Priya Menon: Thank you, Jason, for sharing that. Dr. Cuchel, I'm circling back to you a bit. What is the current standard of care? We have just heard Jason's.

Dr. Marina Cuchel: Yeah. I am truly grateful for Jason to really be so open with his journey on this disease. So, he mentioned there is no real cure for LCAT deficiency right now and we can discuss then what we can do for that. So, let's see, first of all, let's start really very early, what we can do to prevent passing down this condition. And so, because this is an inherited disease, inherited condition it has went to parents pass to the child a defective gene. And so, the risk factor to get this condition is really linked to the law of inheritance. And so if we know that we have a positive family history either for an excess of heart disease or even for renal disease every prospective parent should consider to have a lab test, a blood test to see how are my cholesterol numbers. And if I found that both myself and my husband have low HDL certainly talking to the doctors, seeing prenatal care, understanding what could be the potential consequences are very important, especially again, if we know that there is something that run in the family. So, we can suspect that there is a genetic condition. So, if we are as lucky as Jason was that his mom really advocated to look for the reason why Jason had this very low HDL levels and this was a test that she demanded to do after her husband died at a very young age of a massive heart attack. And so, if we are so lucky to identify your patient with this disease or a person with this disease because he is not yet a patient even before any sign or symptom appear then we really as Beverly was doing trying to start and follow a very healthy kidney friendly diet will be very important because for a patient with FLD Familial LCAT deficiency, the most important goal is to try to preserve the renal function as long as possible because the only thing that we can do once the symptoms appear is that to treat the symptoms, not to treat the cause. And so we know for example right now that some of the factors that may affect the progression to renal disease are associated with high cholesterol and high triglyceride and Beverly was mentioning this to you, so not only kidney friendly diet but also a cholesterol friendly diet to be followed with a heart friendly diet. If necessary some drugs should be given to control the lipids level, like to control the levels of cholesterol like triglycerides that these people have and then of course as soon as we start to see that the kidney may start to get damaged and so if I follow routinely

with my doctor and routinely I do blood and urine testing and then maybe starting as soon as we can drugs that can protect the kidney and unfortunately these drugs are just blood pressure drugs or diuretics because for now we do not have much more to offer. What also Jason mentioned is that usually when you arrive to have end-stage kidney disease then the only option that you have is dialysis or kidney transplant and how Jason alludes to, the transplant doesn't cure the disease because it's not tackling the cause and it's just buying time. And so again very important to maintain a very good diet and lifestyle habits, very important to follow all the prescription medication that the doctors gave it to you. But at the end it is frequently happening as in Jason that you need another transplant and in Jason's case it was after about 10 years after the first one. And so, this is unfortunately what we can do for the kidney. Fortunately as Jason said to you right now usually the corneal opacity doesn't affect too much the vision. But there are few people that are affected, in that case you can consider a corneal transplant. And so, follow up with the eye doctor will be very important and the anemia is just treated symptomatically. So, as you can see, all the treatments that we have now available are only treatments to treat the symptoms, not to tackle the cause of the disease.

Priya Menon: Thank you Dr. Cuchel. Jason, Beverly, do you have any questions for Dr. Cuchel?

Jason Marshall: It's always interesting to me to see what is on the horizon. Technologically speaking is there any direction that we're heading, anything show promise for potential form of therapy for the disease itself instead of just treating the symptoms.

Dr. Marina Cuchel: Jason, this is the million-dollar question, so you know that very very well. So, there are quite a few opportunities that are emerging that are still very far from the horizon meaning that they being tested, first in cells and then in animals and there are very very very few approaches that have reached humans, being tested in people. And when I said very very very few people, I really literally say less than a handful of people that receive some experimental treatment and among this treatment could be recombinant a synthetic LCAT that is the protein that is missing, a synthetic HDLs, but not much much more. So, your approach, I truly admire. You and your doctors are really trying to tackle the cause of this disease after your first transplant, and they tried to see- let's see if we gave, a piece of liver to Jason, can Jason produce the LCAT that is needed to cure and treat the cause of the disease. I mentioned earlier LCAT is produced by the liver, so that was the rationale, let's give him some liver to see. But Jason, as you well know you are the n of 1 to try this treatment and and so it's very difficult when there is an n of 1 to understand if the treatment is valuable or can be further pursued. So, you are absolutely right, there could be different reason why your experiment failed, and one possibility is a testing for LCAT antibodies, but it's a test that doesn't exist. So, there is some research lab, and we are trying to do that but is no simple or maybe your body just rejected this piece of piece of livers for whatever reason, how many transplant recipient had problem with rejection. So we do not know, but that concept is really the base of novel treatment that are in development like cell therapy or gene therapy, but these are still so far away to be used in humans, because first we need to be, it will work in cells, it will work in animals and then if everything goes well, let's try to see if we can test it in real people. And I would like to then just give a shot to one of the biggest obstacle for the development of treatment for rare disease in general, but specifically for LCAT deficiency and it is not only that there are very few people with this ultra rare genetic condition, is that because there are so many people all around the world, we ourself the doctors and investigators and the patient we do not know much why the disease occur, why the cholesterol gets deposited in the eyes and in the liver and not somewhere else. And why some people may develop renal disease, kidney disease and some other not or why some people that have the same genetic defect develop the kidney disease and other no or someone develop the kidney disease very early and some other very late in life or not at all. So, all these questions are key and if we don't know all these pieces, we cannot really build and plan for our clinical trial because we don't even know what to measure, right? We don't know how long will it take for them to developing a renal disease or the opacity in

the eye. And so, for this reason while all the bright scientists that are working preclinically on developing this new treatment, we are really focusing all our attention to learn more about the disease and Jason knows because I always talk to him about that. I really see this as a strong collaboration and important collaboration between the patient, the doctor, the investigators, the advocate to try to put together all these data and try to understand the next natural history of the condition. What are the factors that affect this condition. And so, we have an ongoing study that hopefully goes in parallel to the development of Novel treatment. So, when these novel treatments are available to be tested we know what to look for to see if one treatment is successful or not.

Priya Menon: Thank you, Dr. Cuchel. Thanks Jason. That is a great question. Jason, it would be great in fact because you shared your story with us, your day today challenges, do you have any tips for people who may find themselves in a similar situation, any words that you want to share with them?

Jason Marshall: Absolutely, don't be dismissive of the disease for one. Definitely be proactive in your care Management I would encourage anybody with FLD or FED to get involved in a research protocol such as Dr. Cuchel's as she is doing great work to extend the range of her research and the more people we can get involved and I think she can speak a little more on some of the bureaucratic hurdles that stand in the way of the orphan diseases like this, but the more people that get involved maybe the more successful have in not only understanding the disease and advancing the research from that perspective, but also advancing the research for potential cure. And to that end, Dr. Cuchel, I think you mentioned somewhere around 125 diagnosed cases in the world, are there any kind of understanding of how many undiagnosed cases there might be because of the lack of understanding of the disease.

Dr. Marina Cuchel: Jason, this is an extremely important question, and the honest answer is no we don't really know how many undiagnosed patients may be there. And, I mentioned to you so those 120 cases that are reported in the literature and we know exist are over since the 70 when this disease was noticed, described for the first time until now and man who published a paper is because found a case that is interested in us the opportunity to publish that case and share it with the context scientific and medical community. Many people for example they have FED, and they only think that they do have cloudiness of the eyes, don't even go to the doctor to be tested because they do not have any symptoms. So really, we do not know how many undiagnosed patients or also patient that get diagnosed with renal disease and never understand the cause of it. And so, we believe that is very under diagnosed, we are seeing only the tip of the iceberg and hopefully if we are good on increasing awareness to the eye doctors, to the kidney doctors, to the dialysis center, patient and patient advocate like you hopefully we can increase the amount of people that come out of the woods and as you said collaborate and and try to advocate for the development of cures.

Jason Marshall: And I will say from my perspective from a patient perspective, doctors and researchers such as yourself and others who have been working in this field have done an outstanding job of informing the medical field as a whole because if you go back not more than 15 years when I would walk into a doctor's office and speak with any doctor be a cardiologist, nephrologist, anything a general practitioner, they had never heard of LCAT deficiency, FLD or anything of the kind. But I'm happy to say that these days that is less common. I'd walk in if I see or encounter a new doctor, they have at least heard of it now. And so that is a huge step in the right direction. Thanks to your work and those like yourself and I thank you.

Dr. Marina Cuchel: We need to also many patients like you then goes to the doctors and say this is the disease and please make the effort so I do not have to reach a third transplant sometimes.

Jason Marshall: I'm trying but I can't pronounce most of the words you use, lot to learn to understand them.

Priya Menon: Marina, some of like as we were discussing the information on LCAT deficiency so rare, right as Jason said right now like now things are changing. So where can maybe patients and caregivers go for information on managing the condition because I am also aware like you search on the internet, there is not much out there. So where can people go to find out more?

Dr. Marina Cuchel: Priya, thank you, this is a very important question and we as a treating physician, researcher and everything we should do a much better job. So, theoretically there are two rare disease organization one is not in the United States, one is Orphan and Rare Disease in Europe that if you go in their website and type LCAT deficiency they will provide some information and they will also have the possibility for you to reach and search and link to Centre of Excellence. There is always clinicaltrial.gov that is the government run or the depository of all clinical trials that are conducted or clinical studies that are conducted for every single disease that you can think of but if you also there type LCAT they will come up with a group of studies that are being done with link of contact person. And Jason was mentioning right now, they're starting to be a better understanding at least of the name and so if you go to a lipid specialist, a lipid specialist should really put you in contact if they do not have any direct experience with some of the colleagues that have that experience or some nephrology kidney doctor that knows this disease. I plug the last things for myself. I am available to receive any inquiry. We created a good network of international doctors and researchers that specifically work on LCAT deficiency. So also, if you are in Japan, I can refer you to a colleague in Japan or if you are in Europe there are few groups in Europe or in Brazil in this page. So, please do not hesitate to contact me, I'm very happy to answer any question. If you are a patient, if you are a doctor or if you are a researcher, I'm here and I can be contactable and very happy to help you out.

Priya Menon: That's wonderful Marina and I hope our listeners would definitely hear that and if they have somebody or they need any kind of information they will reach out. So, I think it's time to wrap up today's session. Marina, Beverly and Jason, thank you so much for joining and sharing your stories with us, as Marina said ultra rare disease, LCAT deficiency disorders and I hope this discussion has provided a little bit more information on such a rare condition. We thank all of you, we also thank University of Pennsylvania. This talk will be available on curetalks.com and Penn's website. Thank you everyone and have a great day.

Thank you.