



Sickle Cell Disease

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Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it is a conversation about sickle cell disease with Dr. John Roberts. Dr. Roberts is a Professor of Internal Medicine and the Medical Director of the Adult Sickle Cell Program at the Yale School of Medicine, where Dr. Chagpar is a Professor of Surgery.

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Chagpar So, John, let's start by talking about what exactly is sickle cell disease?

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Roberts Sickle cell disease is an inherited disease of the blood. Red blood cells, which turn the blood red and carry oxygen normally are round and very flexible, and so they can wind their way through very small blood vessels. In sickle cell disease, the red blood cells assume a rigid shape of a sickle and these rigid sickle-shaped cells can cause obstructions in the small blood vessels because they get tangled up one with another and with other blood cells. And that obstruction leads to a failure for the blood to flow into the tissues beyond the obstruction and that leads to the loss of oxygen, which leads to a bunch of problems.

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Chagpar Okay. So, you mentioned that it is genetic, tell me a little bit more about that, who gets this?

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Roberts Okay. So, in the United States, this is really a legacy of the African slave trade. Sickle cell disease is a mutation that arose historically in Africa and also probably in the middle east or India. It is a disease where both the mother and the father have to carry at least the trait of the disease, but they are usually not sick, but if the mother and the father - their child, if the child gets the sickle gene from both the mother and the father, then the child has 2 other sickle genes and all the red cells they make are prone to sickling. And so, whereas the mother and father are not ill, the child is very ill and indeed in Africa today, most of these children die before the age of 5 of infections.

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Chagpar And so, how is that picked up? I mean, is it like the mother is fine, the father is fine, they have a baby and how do you discover that the baby inherited both of these genes and their blood sickles?

02:32.900 --> 03:46.300

Roberts Well, that's a very good question. Actually, since the late 1980s, in this country we have neonatal testing or newborn testing. So, before a baby is discharged from the nursery, the doctors do a pinprick on the heel and get drops of blood on a piece of paper and that piece of paper is sent to a lab and they can test for 60 or 70 different genetic diseases. Where the system falls down in the United States is that that information is then transmitted to the pediatrician who check the baby out of the newborn nursery, but that may not be the pediatrician that the mother takes the child to for well-baby care or the notification may get lost. And so, although everyone who is born in Connecticut in the last 30 years has had testing for sickle cell disease, many people are not aware of their status. As I said, it predominantly effects people of African heritage, and so for people who identify as African-Americans, probably 1 in 10 carries the gene, but they are not sick, but that means that if one of those one in ten who carry the gene has children with another one in ten who carries the gene, then there is a chance that their offspring will have the disease.

03:46.300 --> 04:08.600

Chagpar So, you are telling me that every child has got this test before they leave the nursery. So, every child will have been tested and presumably the reason why we test these children is to know about this so that hopefully there is something we can do about it, but nobody checks the results before they leave the nursery?

04:08.600 --> 04:33.700

Roberts The results are not available. Remember, they are doing 60 or 70 tests, these are soon after a reference laboratory and so the results are not available for weeks at a time, I do not know the exact timeframe. And so, the babies are long gone from the hospital. And then, it becomes the responsibility of the system to get the information to the baby's mother. And often that is successful, but sometimes it is not.

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Chagpar Wow!

04:35.300 --> 04:52.000

Roberts There may be some technical problems to the test, so it may not be 100% effective, but it is a very effective test for identifying people, newborns, with the trait or the disease, and to the extent that people do not know their status, it is a failure of the system to follow up with that information.

04:52.000 --> 05:07.800

Chagpar Right, because you would think that if they test and take quite so long to get done that parents could be notified of that before they left the hospital and presumably plugged into the right kind of resources that can help with this disease?

05:07.800 --> 05:32.500

Roberts People are aware of the problem, but one of the proposed solutions that I am aware of has not been to have a more rapid turnaround time on the test I think because of the complexity of doing the test and the need to batch tests so that they can be inexpensively run and the fact that they are doing multiple tests. So, that is not one of the solutions that I have heard discussed.

05:32.500 --> 05:52.600

Chagpar Yeah. And I mean, I think for our listeners at least in the current environment I suppose it is important to be aware that these tests are being done so that you can follow up with the hospital or the nursery or your doctor or somebody to say "hey, did you get all the tests on my baby and is there anything that I should be concerned about?"

05:52.600 --> 06:23.100

Roberts Yes. I have not seen what these reports look like because I am not a pediatrician, but my understanding is that the reports go from the state lab to the pediatrician that the state identifies as being the pediatrician for that child. Of course, the pediatrician is discharging a newborn from the nursery may not be the pediatrician and may not even be in the pediatrician group that is actually going to care for the child on the outpatient basis, and so the difficulties tracking down the right pediatrician and then having them check down that report, but in principle, that could be done.

06:23.100 --> 07:13.900

Chagpar That's amazing. It is mindboggling to me that that is the case. But in any event, I think for our listeners you should know that your baby if you have a baby in the state of Connecticut is having a bunch of tests done and you might want to know the answers to and so we do not know how long those tests take, but presumably within a month or so if you have not heard back about the results of all of those tests, you may want to call the hospital, make sure that you have your pediatrician's name on that report and/or get the report yourself so that you know the health of your baby. So, let's get back to

talking about sickle cell. Let's suppose that you actually do find out that your baby has sickle cell disease. So, your baby has all of their red blood cells are sickling?

07:13.900 --> 08:40.400

Roberts Well actually, although we can determine that an infant has sickle cell disease or sickle cell trait with a blood test drawn as a newborn, the disease does not manifest itself, babies do not get sick until they are about 9 months of age, somewhere between 9 months to a year in age. And that is because the blood is changing. There are 2 kinds of blood in human development, there is a baby kind of blood and adult kind of blood, and when the babies are born, they are in the midst of transitioning from the baby kind to the adult kind. They only develop problems with sickling when they have transitioned completely to the adult kind of blood, which actually occurs in the first year of life even though it is called the adult kind of blood. So, what typically happens in a child who has not been diagnosed or what parents may be aware of in a child who has been diagnosed with sickle cell disease is episodes of pain and that may manifest as just crankiness, failure to nurse, failure to go to sleep, irritability. There also may be visible obvious signs of inflammation; for example, the hands and fingers can swell up like little red hot sausages and that is a sign of sickle cell disease. The first time may be an infection, of course, infants without sickle disease can develop infections, but children with sickle cell disease are more likely to develop infections like pneumonia associated with fevers. And so, for any of those things, it would be appropriate for the parent to take the child either to the pediatrician's office or to the emergency room depending on how acute the situation and what time of the day this occurs.

08:40.400 --> 09:28.100

Chagpar So, let's suppose that the system was actually fixed such that you knew whether your baby had sickle cell disease or not at the time they left the nursery and granted that they are not going to have any problems until 9 months later when they transition over to having "adult type of blood," is there anything that can be done to prevent all of those issues - the issues of inflammation, the issues of infections, the issues of pain presumably because blood is sickling and oxygen is not getting to the tissues where it needs to get to, is there something that can be done proactively if you know that your child has this problem to prevent them from getting all of these downstream issues?

09:28.100 --> 10:33.900

Roberts Yes, indeed there is. It is not a cure, but it is a preventative and of course before a child gets to be 9 months of age, the parents should have taken them to the pediatrician for the normal series of baby shots, which started about 2 months of age and so there would be multiple opportunities there for the pediatrician to educate the mother about what the manifestations of sickle cell disease are, how the mother might learn that the kid was sick and what she should do in those situations. There is a medicine called hydroxyurea and pediatricians are increasingly recommending that babies start that drug who have sickle cell disease and so they might typically start a baby on that drug at 9 months of age and that drug can dramatically reduce the problems of sickle cell disease. So, an infant put on

hydroxyurea at 9 months of age might live out their entire childhood without ever having to have an acute care visit for problems related to sickle cell disease. On the other hand, it is not a perfect medication and those children likely would have 1 or 2 problems but many fewer problems they would have had if they were not on hydroxyurea.

10:33.900 --> 10:47.100

Chagpar And so, it can prevent the kind of severity I suppose of these episodes, but they still have blood cells that sickle and so, they still can get issues?

10:47.100 --> 10:47.800

Roberts Yes.

10:47.800 --> 11:01.900

Chagpar And so, if you have those issues right like, so my understanding is the blood sickles, so then it can block off the blood vessels so then oxygen cannot get to tissues where it needs to get to which is bad?

11:01.900 --> 11:01.100

Roberts Yeah.

11:01.100 --> 11:10.900

Chagpar So, what do you do about that in an acute crisis, like I mean if your fingers are swelling up like sausages that does not sound like it is a good thing John?

11:10.900 --> 12:17.300

Roberts For the acute crisis, we generally just treat infants or adults with pain medicines and a lot of fluids so we do not people to be dehydrated and have the cells trying to get through the blood circulation in narrowed sticky blood. On the other hand, there is research going on to find medicines that will interrupt the acute crisis, but we do not have those medicines available yet. Sometimes, people are transfused at that time, particularly if their red blood cell count is very low, but there is a danger if someone is going to have a lot of those episodes if we give them blood transfusions every time they have an episode, we are getting to long-term problems with repeatedly exposing people to other people's bloods, problems where the patient gets to a state where their body recognizes blood from other people and the white blood cells in the patient eat up the red blood cells from the donated blood

and then we cannot transfuse people effectively. So, for the acute episode, the primary treatment is hydration and pain management.

12:17.300 --> 12:27.900

Chagpar So, really just kind of symptomatic kind of help the patient to get through the pain, help them to be well hydrated and wait and see?

12:27.900 --> 12:29.300

Roberts Yes, that's correct.

12:29.300 --> 12:57.900

Chagpar One would think that if oxygen is not getting to tissues because it is blocked off because of these sickled cells, tissues could die and you could end up with like, I could think like if you had blood not getting to your kidneys, you could go into kidney failure or if blood is not getting to your lungs, you could have difficulty oxygenating other tissues or bloods not getting to your heart that you could end up with heart dysfunction, what about all of that?

12:57.900 --> 13:34.600

Roberts Well, you are right on target. Although we think of it as a blood disease and it is kind of cared for by hematologists, in fact it effects the blood vessels and then the organs of the entire body, and so it can affect the brain, the eyes, the lungs, the liver, the kidneys, the spleen, the skin and so in all of its manifestations, it is a devastating systemic disease and even today people in United States typically live into their 40s but they are unlikely to live past 50.

13:34.600 --> 13:45.500

Chagpar Oh wow! Well, we have to take a short break for a medical minute on that very somber note, but please stay tuned to learn more about sickle cell disease with my guest, Dr. John Roberts.

13:45.500 --> 14:00.900

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14:00.900 --> 14:47.100

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14:47.100 --> 15:28.300

Chagpar This is Dr. Anees Chagpar, and I am joined tonight by my guest Dr. John Roberts. We are talking about sickle cell disease. Now, right before the break, John, you were saying, we were talking about how sickle cell disease is this disease where the red blood cells sickle and essentially they block off blood vessels so that oxygen cannot get to tissues and you end up with all kinds of end-organ issues; whether it is in your brain, or your eyes or your lungs or your liver or your spleen or your kidneys and this is really a devastating things. One other things that you said before the break that I found dramatic was that very few people live beyond the age of 40 or 50, is that right?

15:28.300 --> 15:47.500

Roberts Beyond the age of 50 is uncommon, it is not rare. I mean, I have patients in my clinic who are in their 50s and 60s, but I have many, many more patients who are in their 20s, 30s and 40s, and when our patients unfortunately die, they are often in their 20s or 30s or early 40s. So, it is a devastating disease there is no question about that.

15:47.500 --> 15:50.900

Chagpar And they die because of all of that end-organ issue?

15:50.900 --> 16:01.000

Roberts They die because of complications in organs other than the blood typically. So, they die of strokes or heart failure or kidney failure or overwhelming infections.

16:01.000 --> 16:33.200

Chagpar And we talked about the fact that, you know, all babies in Connecticut are diagnosed or at least have a test to see whether or not they have this disease. But, what we said was that really treatment was kind of symptomatic - pain management, fluids, there has got to be something that we

can do to prevent this devastating disease from killing off people. Is there no cure, is there no treatment that will make your cells not sickle?

16:33.200 --> 20:50.400

Roberts There are a few more things that we can do now and there are some exciting possibilities in the future. So, the only curative therapy we have for sickle cell disease now is a bone marrow transplant. That involves giving the patient, the person with sickle cell disease strong chemotherapy type medicines to sort of kill off their bone marrow cells where the red blood cells are made and then infusing into that person bone marrow cells that have been harvested from a donor. And those donor blood cells infused into the person who had sickle cell disease as they grow up, the person becomes somebody who no longer has sickle cell disease because they are operating off the blood system that they got from the donor who is healthy. There are a number of problems with this- one, there is some risk with the procedure, two- the best outcomes are when the donor is both a full sibling, brother or sister of the patient and also is what we call a complete match, which is we can look at certain proteins that are expressed on the blood cells of the donor and the patient and we want those to match up, and if they do not match up, the prospects are much less favorable for the outcome. Only about one in five people with sickle cell disease in the country have an appropriate sibling potential donor. So, it is not going to be able to cure most people because only one out of five people are even a candidate. But it is being used in many fewer than 1 out of 5 patients and so one of the agendas of particularly the pediatric blood community, hematology community, is to talk more with parents about the possibility of a bone marrow transplant for their children. Now, we can do bone marrow transplants with donated red blood cells that come from a non-relative, but there are more risks involved with that and I would consider that to be a research procedure, and actually at Yale in the pediatric hematology department, Dr. Nikita Shah is participating in research studies of bone marrow transplants for sickle cell involving unrelated donors. And so, she has done transplants on 8 persons with sickle cell disease in the last year or so, last several years, and several of those were in people who did have a brother or sister who was a donor, but also some of those were in people who did not have a complete donor. Now, gene therapy is another exciting thing and there was a report a couple years ago of a patient in France who was cured with gene therapy for sickle cell disease, but most people feel it is not quite ready for prime time, there are a lot of concerns about what the potential risks and downstream effects of gene therapy may be. There was an episode about 20 years ago when we were curing acute leukemia with gene therapy and then unfortunately in 2 or 3 years, those children would then come down with another kind of leukemia and we do not want that to happen with sickle cell disease. Then, there are a number of drugs, which are sort of like the hydroxyurea that I talked about which sort of modify the ravishes of the disease, but they do not really make the disease go away, and a lot of these are being developed now by drug companies and it is a very exciting time because some of these drugs I think are going to be very good, but they are not yet available yet. We do not have any of those research studies, but at the University of Connecticut, Dr. Biree Andemariam will be opening a study of one of these very promising new drugs in just the next few months. And then, there are other approaches to potentially cure the disease with either different types of gene therapy, Dr. Peter Glazer at Yale's Department of Therapeutic Radiology is actually interested in gene therapy with a totally novel approach using drugs which are designed by him in conjunction with people at Yale Bioengineering. And there are other approaches to drugs, actually I talked earlier about the baby hemoglobin gene is still in the person and if we could just get the baby

hemoglobin gene active again in adults with sickle cell disease, we could greatly reduce the impact of the disease. So, there is a lot of promising research avenues being explored now, much more than was 10 or 15 years ago and I think things are going to be delivered to the clinic in the next 5 to 15 years. It is an exciting time, but it is still a very challenging time with people who are living day to day with a problem of sickle cell disease.

20:50.400 --> 21:48.600

Chagpar It is great to hear that there are actually options. But, just to go back through some of those - so, the bone marrow transplant, I mean, that is something that we have heard about that has been used in cancers for example, but one would think that in sickle cell disease being a genetic condition, the fact that you got sickle cell disease meant that both of your parents had a sickle cell trait, and so, you happen to get the sickle cell gene from both of your parents. And so, you would have to a sibling who got the other non-sickle cell gene from both parents, is it possible to get a bone marrow transplant from a sibling who had sickle cell trait, who maybe got a sickle cell gene from one parent but not from the other parent, so they are not going to manifest any of the symptoms, that is better than having sickle cell disease?

21:48.600 --> 22:02.000

Roberts That's been tried, but for reasons that I do not understand, it has not been especially successful. And so, it is not recommended. There may be research centers that are trying that on a research basis now, but as a standard off-the-shelf treatment, it is not offered.

22:02.000--> 22:36.200

Chagpar And then the other thing is, you know, with regards to unrelated people, what is the issue with that? Why is that just something that you would do on research and I get that it might not be ideal, but you know, we transplant for example entire organs right, we give people heart transplants and liver transplants from completely unrelated people and people then can live after needing these organs, so how come we cannot do that bone marrow in sickle cell?

22:36.200 --> 23:46.700

Roberts Yeah. Well, that's a good question. So, when we are dealing with a child or adolescent with sickle cell disease, we are talking about giving them a curative therapy with a transplant so that their life will be better, but if we do not do the curative therapy, they are likely to live into their 30s or 40s, maybe their 40s. If we do do the transplant therapy, there is always a risk with the transplant that people will die of complications of the transplant. Now, with changes in the way we do transplants, if we do it with an ideal donor, that is a full sibling, who is a complete match, basically people should not die of the transplant procedure anymore and we have known that for a few years now. But if we do that with an unrelated donor, it remains the case that the risk of dying of complications of the

procedure is in the range of 5%, maybe 10%. And so, it is tough to sell parents on a procedure that potentially would allow their child to live a normal life span, but on the other hand might cause their death in the next few months, whereas otherwise they would live into their 20s, 30s or 40s, it is a very difficult decision for people to make.

23:46.700 --> 24:21.600

Chagpar Well, could you not delay that until people were in their 20s, 30s or 40s and looking at eminent demise anyways, you know, they have graduated college, they started their career and you know most people are not going to make it although you have had some patients make it into their 50s and 60s and they are thinking to themselves, you know, choose a 5% chance of death from a potentially curative treatment might not be so bad if you are telling me that I have got a, I do not know what the percentage is, chance of dying in the next year or two anyways?

24:21.600 --> 25:17.700

Roberts Well, I have had 2 patients in my practice who were in their early 20s go for transplants in the last few years, so that does happen. On the other hand, the older a person is, the more likely that they have now accumulated damage to again the brain, the lungs, the heart, the liver, the kidneys, in the spleen and so the risks of transplant are higher because the transplant is a pretty dramatic thing that we put people through, and so as people age, either doctors may no longer offer it or the risk of bad outcomes goes up a little bit. And just going up a little bit is enough to turn people off. And then, as you think about it from a psychological standpoint, as a senior when I think, well if I was in college and I had sickle cell disease, I would probably finish college and then I would go get a transplant. When I was in college, I was not particularly thinking about preventing things that would happen to me 20 or 30 years from now.

25:17.700 --> 25:30.700

Chagpar This is true. And I suppose the other thing is, if you are getting somebody else's bone marrow, even if you are a perfect match, do you still need to be on some sort of immunosuppressant just so that you do not reject their bone marrow?

25:30.700 --> 25:43.800

Roberts Yes, that's a good point I had not raised that, but everybody is on immunosuppressants immediately after the transplant and most people remain on some kind of immunosuppression for the rest of their life.

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Chagpar Which is not so much fun anyways?

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Roberts Correct.

25:46.100 --> 26:12.200

Chagpar So, that might be another downside. Now, then you talked about gene editing. Now, tell us more about what exactly that is, because you know there are stories about people messing with people's genes and designer babies and that is all kind of getting a little out there, how exactly does gene editing work, I mean is this a therapy that is actually in practice now, tell me more.

26:12.200 --> 28:32.800

Roberts So, there is sort of 3 things you can do from a genetic standpoint. One is, you can just add a normal gene. And so, now that person, and the way you usually get that normal gene into the person's baby red blood cells, the bone marrow cells are going to make the adult red blood cells is with a virus which infects the red blood cells. So, you package in the virus, in a test tube, you package in the virus a normal gene and then you inject the virus into the person's body and the virus goes all over their body but it gets into the bone marrow cells and affects the bone marrow cells and then inside the bone marrow cells, the gene will get out of the virus and it will be expressed and so now you will be making normal hemoglobin and sickle hemoglobin at the same time, and that person would look to a hematologist like somebody who had sickle cell trait because if you analyze their cells, some of them are going to sickle and some of them not. One of the disadvantages of that is that the virus can also insert itself in a lot of other places in the normal genetic material and as I mentioned earlier, we are concerned that that virus insertion in other places could make other genes run amok and cause problems like cancer. Then, the second way you can do it is to actually, as you said, edit it so you can use a thing called crispr technology, try and, again you have to send it into the cells mainly with a virus, you send in the cells and what you are sending in is an editing machine where you are supposed to go exactly to where the abnormal gene is and cut out the abnormal gene and put in the replacement gene, which is normal. That has not been successful in humans that I am aware of yet, and there is also a concern that it may do this not only in the right place but also in some other places which are not right place and again we are concerned that that could make other genes go awry. And then, the third way would be to somehow as I mentioned earlier genetically fool the bone marrow cells to go back to producing the baby hemoglobin. And the advantage of that would be that it would be a normal gene being produced and the problems with that has been it is technically difficult to do and you might unleash a bunch of other genes being expressed which we do not want to be expressed in adult life, you know, abnormal tissue growth and stuff like that. So, I think most people think these are all soluble problems, but they have not been solved to date.

28:32.800 --> 28:49.600

Chagpar And so, then then the third bucket of possible solutions to sickle cell disease which now after thinking about the disadvantages of the other two might be the most promising is, are new drugs, but these drugs are not perfect.

28:49.600 --> 29:13.700

Roberts So, we have 2 kinds of drugs. We have drugs which are supposed to sort of allow the body to put up with the sickling cells better and we have drugs which are actually supposed to cause the expression of baby hemoglobin, and the baby hemoglobin drugs are harder to design but would be more of a homerun. The bandage drugs put a Band-Aid on it are going to be here very quickly but they are not going to do so much.

29:13.700 --> 29:42.100

Dr. John Roberts is a Professor of Internal Medicine and the Medical Director of the Adult Sickle Cell Program at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on Connecticut Public Radio.