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Released: 12/22/2022
Valid until: 12/22/2023
Time needed to complete: 1h 20m

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Reducing Time to Treatment and Care for Farber Disease: How Do We Achieve Our Goals?

Announcer:
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Dr. Mitchell:
So thanks for joining us today. My name is John Mitchell. I'm a biochemical geneticist at the Montreal Children's Hospital in Montreal, Quebec. And we're here today to talk about Farber disease and I have with me Dr. Paul Harmatz. So, I would like if he could tell us a little bit about himself.

Dr. Harmatz:
Thanks, John. I'm Paul Harmatz. I'm a Pediatric Gastroenterologist at UCSF Benioff Children's Hospital, Oakland. I spent most of my time working with, mucopolysaccharide storage disease so Farber is a bit of field and I've collaborated very happily with John as our Canadian expert in mucopolysaccharide disease. So, appreciate coming together and talking about Farber and learning from John on this really devastating but extremely rare and difficult to recognize disease. John.

Dr. Mitchell:
And I think that was one of the things we wanted to talk about, Paul, is, you know, it is a, it is an ultra rare disorder and it is quite devastating. There is quite a bit of heterogeneity. How do most of the patients come to you in your practice or how have they come to you, or how do you think they could come to you in your practice?

Dr. Harmatz:
Thanks, John. The, I mean, the third option is probably the most likely situation. Most of the patients that we've seen have come through for the natural history study. When you, when you work with these incredibly rare diseases you, it's hard to find single centers that have taken care of a lot of the diseases.

And until there's a natural history or a clinical trial for therapy, you don't get real pockets of the disease, unless it's a basic science interest that drags you into that sphere. So, but the range of patients that we've seen have been severe with onset early and by two or three severe contractures, hoarseness and nodules, tremendous pain, very high inflammatory state. If you ran a sed rate, you would come out a hundred or more. You just have to be very careful. You don't let this necessarily fall into one of the autoimmune or JRA, juvenile idiopathic arthritis categories, and have to keep thinking metabolic. It's fortunate if it moves to a geneticist or a metabolic person first before it moves to a rheumatologist, because they're used to dealing with extremely rare syndromes than driven by underlying metabolic genetic disease. So.

Dr. Mitchell:
Yeah, I think-

Dr. Harmatz:

Your experience too, John?

Dr. Mitchell:
I think that's been my experience. Most of my patients actually, and we're talking a very small number. I've seen five patients with Farber and most of them have come out of rheumatology. And it's really my relationship with the rheumatologists in other lysosomal diseases, that's helped a lot. And they don't necessarily know what the disease was, but they said it's not in our wheelhouse, we think it's more likely to be in your wheelhouse.

So, having that good relationship with the rheumatologist has certainly helped get those patients to me. Perhaps not as quickly as we would like, but they do end up in the right place eventually. Once they do come to you, Paul, what are the different types of treatment options? Because we don't have any disease modifying therapies so far. So what do you think we can offer these patients with this very devastating disease?

Dr. Harmatz:
It's limited. Mostly supportive therapy. We try to control pain with anti-inflammatory, non-steroidal medications. We try to bring in physical therapy. We try to ask sort of gastroenterologists or pulmonologists to come and assist with particularly nutrition, is a very difficult area for the severe patient. And pulmonary has to continue to monitor the airway and decide at what, you know, is it stable or does it actually need a tracheostomy.

I've had one very good outcome with a patient who had severe disease, but still neurologically intact. And there was a stem, hematopoietic stem cell transplant. A good outcome of the transplant with resolution of nodules, pain moves under complete control. The hope is that, as I mentioned in my individual lecture, that it's really supplying the enzyme whether it's infused, given, generated by a gene therapy or by a stem cell transplant. Hopefully we'll get similar responses, systemically. The brain may be a different challenge and we have to look eventually at enzyme, so it may transfer to the brain or a direct gene therapy that's brought in to focus on the brain. So, it's almost, you have two pictures. How to treat the systemic disease and how to treat the CNS disease. Right now, it's mostly supportive, but I was amazed at the transplant effects.

Dr. Mitchell:
Yeah. And I should clarify, with disease modifying, I think if we do do transplants, we can modify that peripheral, those peripheral manifestations, but it has not had any impact sadly, on the neurodegeneration. And that's where we're really lacking something in terms of something to offer to these families, which is somewhat different from what we would expect with some of the other neurodegenerative lysosomal storage diseases where we do see effect on transplant. And yeah, I would like to echo your comments on tracheostomy or perhaps also G-tubes. A lot of these patients will have reflux and that can contribute to their lung pathology with recurrent aspiration pneumonia. So if we can find a different way to allow them to feed and absorb that nutrition, which is something that may also, the underlying disease may also play a role in the GI system. So, I think if we can get them to grow and absorb that food, and make sure they're not putting their lungs in danger, that's certainly a benefit as well. Pain is-

Dr. Harmatz:
How have you dealt with- Do you see the SMA-PME group or a Farber?

Dr. Mitchell:
I've seen one patient with SMA-PME and this is for those of you who aren't aware, this is sort of a different disease that is caused by the same gene defect and there is some crossover, and the patient I saw did actually have the spinal muscular atrophy, but he did have some developmental nodules as well.

So I think this is where we need to look more at this population and see if there is more crossover than we think. They're mainly followed by the neurologists, so it might be that some of these nodules might be going missed. They're not being seen necessarily by rheumatologists, or for that matter, not necessarily by geneticists or by a chemical geneticists, as well. So I think this is something that we really need to look at in more detail. And with the upcoming enzyme replacement therapy, the question would be, would this have any benefit for those patients with primarily a neurological presentation. And that's where we might get into the transfer of this enzyme into the CNS by various methods which may need to be used.

Dr. Harmatz:
Have you, do you find that the neurologists are using whole exome or whole genome methods? Is this going to speed up diagnosis in rheumatology or neurology? Or do they have to reach the geneticist to find this?

Dr. Mitchell:
So, I think they do in some of the larger centers and certainly our neurologists are very happy to order panels and the acid ceramidase genus is actually on some of the SMA panels now. So that can lead to earlier diagnosis rather than waiting for the geneticist to receive

the consult. And I think that can be beneficial in a number of ways. These types of panels where we're thinking about a very rare disorder, but we don't necessarily think specifically about Farber. The panels can include this gene in some of the lysosomal panels as well. So, this can lead to earlier diagnosis, certainly for our patients thinking about this. And this is, one of my patients did come through a rheumatologists who ordered some of this testing. So I think that can be beneficial as well.

Dr. Harmatz:
I think the holy grail will be to have newborn screening once we have a therapy and we will not miss these patients and we'll treat them.

Dr. Mitchell:
Yeah. Well thanks very much, Paul for joining us today and having this discussion. I think this is a very rare disorder, but one that really needs a lot more attention. And we need to learn a lot more about the natural history, before we can get these earlier diagnoses and progress. And do you have any more thoughts on that?

Dr. Harmatz:
No, I think it's, just remembering the triad hopefully will trigger everybody to refer to a geneticist or send a panel or a whole, an exome. So if you see nodules, you have to move outside your comfort zone with autoimmune arthritis and think metabolic disease. Just the same with

Dr. Mitchell:
Yeah.

Dr. Harmatz:
Sidney Farber had the same debate. Is this inflammatory or is it genetic?

Dr. Mitchell:
Yeah.

Dr. Harmatz:
I think we have to find these patients early and hopefully people will stay aware. And I thank you. It's been a pleasure talking to you, John.

Dr. Mitchell:
Always a pleasure, Paul.

Dr. Harmatz:
And we will talk again.

Dr. Mitchell:
I'm sure we will. Thank you very much.

Announcer:
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