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

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# Farber Disease: Symptom Identification and Timely Diagnosis

**Announcer:**
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**Dr. Harmatz:**
Hello, I'm Victor Paul Harmatz. I'm a pediatric gastroenterologist at UCSF Benioff Children's Hospital, Oakland. Today we will spend some time talking about a very rare but important and clinically significant lysosomal storage disease, and this is Farber's disease. And I always like to deal with history. It brings to life the disease process. Rather than memorizing characteristics, you can relate it to famous people. And Sidney Farber, who was an immunologist, pathologist in the 1940s, '50s, '60s at Boston Children's Hospital, first presented a case in 1947 at a Mayo Foundation lecture and then in 1952 reported three cases. And in a '57 publication, they had a very detailed biochemistry evaluation of these three cases.

So overall, he called this a lipogranulomatous disease. It was lipid in basis, and the storage, foamy storage, formed granulomas that he could see in variety of tissues. And he sort of wondered if this is an inflammatory disease like Hand-Schuller-Christian, or is this more an inherited storage disease like Niemann-Pick disease. And it probably is more on the secondary. And he said, you know, "These three cases are quite similar, but the next 20 may be very different," which to some extent we found is true. And so the three cases he described all survived less than two years.

They had the classic features that John, the triad that John Mitchell emphasized in another lecture, the subcutaneous nodules, the joint involvement, and the hoarse cry, plus multiple other findings. When they looked at the biochemistry, they saw the granulomas, the foamy cell infiltration in many, many tissues. And the storage tissue was sphingomyelin that they picked out. So this overview slide on Farber disease, it is lysosomal storage disease. It is a sphingolipidosis that we mentioned. It's autosomal recessive, which is true of most of the lysosomal storage diseases. Although we have other rare particularly X-linked forms of lysosomal storage disease. It's due to an mutation, ASAH1 gene mutation. And I'm sure that Dr. Tuchman emphasized this in his lecture.

This gene mutation leads to ta deficiency of acid ceramidase enzyme. And this deficiency of an enzyme, which you can see in this diagram, leads to an inability to digest ceramide. So you have a buildup of of ceramide, which has generally toxic properties within cells. And it's extremely rare. It has a large continuum, progresses with age, all of which John Prout and Dr. Sutton emphasized in their talks. The two forms that have garnered the most interest probably in the last 10 years are classic Farber disease, which we recognize as a continuum and now accounts for many of the types that ran all the way from one to seven. It's really easier to think of it as a continuum.

In a separate disease called SMA-PME, spinal muscular atrophy with progressive myoclonic epilepsy, and, again, they may just be continuum, we tend to see there are two. There's an alpha unit and a beta unit and subunit in the enzyme. And we tend to see more of the SMA-PME in the alpha subunit. In Farber, we see more in the beta subunit, but this is not 100%. And Farber itself has CNS abnormality. SMA-PME has this muscle weakness, this spinal muscular atrophy, and a myoclonus, myoclonic epilepsy. It tends not to have cognitive till full-blown seizures emerge.

So, very different clinical patterns, possibly on a continuum, all due to the same gene. But most of our focus is really in the Farber side in the rest of this lecture. So these are some pictures from the classic symptoms that we see, the hoarseness and weak cry, dysphonia. You can see the storage within the airway and affecting the larynx and producing these symptoms. You see the classic nodules which form over the extensor tendons. You can see these same nodules on an ear, on a foot. They can be very painful without touching. They can be painful only with touching. There's a lot of variability depending on the severity of the disease on the spectrum. And then this figure outlines the numerous organs that are involved in Farber disease and is a good, If you're looking at the totality of the patient, you can see that it's not just this classic triad. But keep in mind the triad for recognizing and diagnosing this disease. So emphasizing we have rapidly progressive all the way to slowly. Adult-recognition disease presents in the 30s, 40s, 50s, and patients that are presenting in the first couple of months of life and have very rapidly progressive disease and deaths. So these are nodules on a patient thought to have moderate disease. And here's a 28-year-old with a few nodules, a much more slowly progressing disease.

Diagnosis of this disease. The most important step, especially when you're dealing with a disease of one in a million, is to try to recognize the triad, the hoarse cry, the joint contractures. And as soon as you have nodules, it's hopefully a giveaway. Although people with sort of moderate progressive disease in the five to 10-year age range, they're looking at juvenile idiopathic arthritis and sort of completely off track from an inherited metabolic disease.

So, look. Anything that looks unusual, and geneticists now have become very good. If they don't land on a diagnosis very quickly, they moved to that, the third diagnostic technique, which is to send a whole exome or a whole genome and come up with a diagnosis. Traditionally, it really confirms what you're seeing genetically, is to be able to obtain enzyme analysis. It guards against the possibility that you have a mutation that just is there but does not affect digestion of the product. And the same is true with enzyme analysis. You can have an enzyme that can't digest the substrate, the artificial substrate that we're presenting.

So we have pseudo deficiencies. We have mutations that have never been seen before, and their clinical significance is unknown. So we encourage people to try to use both, and we hope that there'll be more enzyme analysis available in the future in the United States and Europe. So right now it's not as easily obtained as any of the other frequently seen lysosomal storage diseases. And I'll finish with this final slide just to introduce you again historically. This is the grand dame of lysosomal storage disease therapies, Elizabeth Neufeld. At the time, she was at NIH for many, many years. But in the sort of late '60s, early '70s working with Fratantoni, they discovered that when they mixed cells from a patient with Hurler disease with cells from a patient with Hunter disease, the cells could secrete a material that would cross-correct.

And in the '70s, all of the biochemists descended and isolated the enzymes that were responsible for this cross-correction. And ultimately, this concept drives all of the enzyme replacement therapies that we have for different diseases. It really is the basis for stem-cell transplant works. You have cells that are making enzyme that migrate and deposit in organs, secrete enzyme, and are able to correct locally. It works on the same basis with gene therapy. You have cells that are infected and are making the gene therapy and have the ability to make enzyme and secrete it to be taken up by adjacent cells, moved through a receptor, transported through the cell to a lysosome to do their work.

So, the future looks really bright. The same paradigms can apply to Farber disease, and we look forward to early recognition, which is critical, and then effective therapy. So ultimately I would predict we'll ask for newborn screening once there's an effective therapy in place, and that we will, all of the recognition will speed up, and we'll have these patients identified in the first month of life. So, thank you. I hope you've enjoyed this introduction to Farber and will find hopefully your one or two Farber patients in your pediatric careers. And thank you.

**Announcer:**
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