## Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/farber-disease-a-rheumatological-perspective/14946/

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

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

---

# Farber Disease: A Rheumatological Perspective

**Announcer:**
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

**Dr. Mitchell:**
Thank you for joining me today. My name is John Mitchell. I'm a Pediatric Biochemical Geneticist working at the McGill University Health Center in Montreal, Canada. Today, in the short talk I hope to familiarize you to Farber disease, it's presentation, and the treatments that may be beneficial for this ultra-rare disorder. I'd like to start out with a case presentation. This is a young boy that came to me at approximately two years of age.

The parents had noticed at seven months of age that he had significant pain when they tried to manipulate his hands. He held his hands in a somewhat clogged position. And when they tried to straighten them, he cried out in pain. The swelling was noted by the pediatrician at 11 months, and he was referred to rheumatology. He was presumed to have a severe form of juvenile idiopathic arthritis. His inflammatory markers, RF and ANA were negative. He was started under naproxen, methotrexate and folic acid. He had a good initial response with increased movement but had the continued pain. He was increasingly difficult to handle. When he was handled and picked up, he started to cry. He had normal X-rays of his hands, feet and knees. And by the time 14 months came around, he started to develop some nodules which we can see here on the pictures.

The nodules were over the extensor surfaces of the hands, but we also had nodules on the back and on the ears and on the legs as well. The rheumatologist felt that this was not consistent with the JIA diagnosis and decided to refer him to genetics for his poor response to therapy. Genetics noted a mild hepatomegaly and coarse facial features. They thought about some of the lysosomal storage diseases and asked for a panel which included the genes involved in lysosomal function. As part of this panel, it was noted that he had a mutation in the ASAH1 gene. This is compatible with acid ceramidase deficiency or Farber disease. We can see from the family tree on the right-hand side here that there were also two maternal cousins with similar features who were later found out to have the same mutations and the same disease.

So, what is Farber disease? Farber is an ultra-rare, lysosomal storage disease marked by significant inflammation. We see here that the ASAH1 gene mutation leads to acid ceramidase deficiency and ceramide accumulation. The ceramide accumulation leads to significant inflammation which is macrophage driven, both local and systemic. The classical triad for Farber disease is polyarticular arthritis, subcutaneous nodules, and a hoarse voice. However, these symptoms may not appear altogether which can lead to delay in the diagnosis. We can also see involvement of the central nervous system and this is primarily manifest as developmental regression. The developmental regression can occur anywhere from two to three years of age, and it only occurs in the most severe enzyme deficiency patients.

This patient likely had a more moderate presentation. There is a wide heterogeneity features. They can also have ophthalmological manifestations such as corneal clouding or cherry red spots. Pulmonary involvement can include aspiration pneumonias and they can

have skeletal involvement with osteoporosis, erosions or even osteolysis later in life. Gastroenterological manifestations can include failure to thrive. You can see here from left to right the variable heterogeneity of these children with this disorder. On the left-hand side, we see a young baby with a rapidly progressive form of this disorder. This has CNS involvement and pulmonary involvement and will often lead to death in the untreated patient at around three to four years of age. Our boy is a second picture over from the right and likely has a moderate presentation. You can see the boy on the right and the girl on the very right hand side who have a more slowly progressive form. Usually there are manifestations in the first decade of life, but these manifestations may be quite minimal. The girl on the very right-hand side was followed in a rheumatology clinic and had some arthritis and some nodules, but little other manifestations. How do we manage these symptoms? It's clear that pain management is critical to the quality of life. Stem cell transplantation has been used in the past for treatment of Farber disease. This can cause a resolution of the inflammatory aspect of Farber disease in the periphery, but has no impact on the central nervous system involvement. Hematopoietic stem cell transplant that is quite a aggressive form of treatment.

So, there are other treatments that we can use and we've had some success with anti-inflammatory medications. Tocilizumab, which is an interleukin 6 receptor antibody, has been symptomatic therapy used to the greatest effect to date. There's a clear reduction of erythema and induration around the nodules as well as significant reduction of pain. We can see this decrease erythema both pre-Tocilizumab and post-Tocilizumab. You can see the resolution of the erythema, however the nodules remain. There's not a lot of experience with tocilizumab in Farber disease.

So, we talked to a number of colleagues around the world and we found five patients who had received tocilizumab. There was a clinically significant reduction in pain in all of these patients. We had ESR levels in four of the five patients that we studied. And we saw that the ESR was reduced by tocilizumab therapy at both one and six months. There was no change in the progression of the disease. So if these patients were going to develop neurodegenerative disorders or pulmonary disorders, this did not have an impact. But it did give a lot better quality of life and these babies and young children were much more easily handled by their parents. We have done a natural history study as well looking at Farber patients. And this is a very rare disorder with only 160 cases reported over the last 50 years. However, a recent multinational natural history study revealed 45 patients that were detected in a relatively short period of time.

So, it's likely that this is more common than previously thought. And what is quite significant about this as well is approximately half of these patients were initially misdiagnosed with juvenile idiopathic arthritis. We can see from the cartoon on the right-hand side here that although 30% of the patients were of the severe form, there was approximately 70% of patients who either had a moderate or attenuated form. And these are the patients that are more likely to be misdiagnosed with JIA. So in conclusion, Farber disease is a rare progressive multisystemic lysosomal storage disease that can often present with severe joint pain and inflammation. It's often misdiagnosed as juvenile idiopathic arthritis. But once the diagnosis is confirmed, anti-inflammatory therapies should be considered to reduce pain, improve joint function and improve quality of life. Although treatment with anti-inflammatory medication can reduce this pain, it doesn't change the disease progression in the severe form. So it's quite clear that new disease modifying therapies are necessary.

So there is a enzyme replacement therapy with Aceragen that is in development. This is quite similar to other lysosomal storage diseases where enzyme replacement therapy has had a significant impact on reducing the burden of these disorders. This is a treatment that can be given as an intravenous infusion and the enzyme can clear the accumulated ceramides. The first in-human trial is expected to start in 2023. If you have patients that you think may benefit from this trial, you can contact me at the following address. So I thank you very much for your interest and your time today and I hope you enjoyed this talk.

**Announcer:**
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.

To receive your free CME credit, or to download this activity, go to ReachMD.com/**CME.** Thank you for listening.