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

The Role and Limitations of Hematopoietic Stem Cell Transplantation in Farber disease

Announcer:
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Dr. Mitchell:
Thank you for joining me today. My name is John Mitchell. I'm a biochemical geneticist at the McGill University Health Center. I'm going to spend a few minutes talking about the role and limitations of stem cell transplantation in the ultra-rare Farber Disease. I thought I'd start out with a case presentation. This is one of my young patients who presented at three months of age to the emergency room. Her parents came to the emergency room because they were having difficulty trying to cut her nails, and what was actually happening is, when they were trying to straighten her hands, she was crying in pain. The ER doctor noticed that there was swelling and redness in the PIPs and DIPs in her fingers. She also had pain moving her wrists and toes.

They noted that she was breathing quite noisily, and had a hoarse cry. Because of the involvement in the joints, they referred her to rheumatology. In the next month, she started to develop some nodules. The nodules were present on the extensor surfaces of the hands and in other places on the body. When the rheumatologist saw her, they decided that this was not something that they thought was in their ballpark. The nodules and other features were more severe than what they would see in GIA, and they felt that this was someone that needed to be seen by genetics.

So, they referred her to me. This girl manifested some of the classical symptoms of Farber disease, and we see here, on the right-hand side, she had a polyarticular arthritis, she had the subcutaneous nodules, and hoarse voice, which are really indicative of Farber Disease. We're not sure really how common this disorder is because there's only been about 150 cases described since it was initially described in 1950s. It's an ultra rare lysosomal storage disease that's marked by significant inflammation.

We know our young patient had the classical triad for Farber Disease, but these symptoms may not appear altogether, and this can lead to delay in diagnosis. Similar to other lysosomal-storage diseases, there can be multisystemic involvement. One of the main features of this particular disorder is, in the patients that have a severe disorder, they can have CNS involvement. The CNS involvement, similar to some other lysosomal storage diseases, can present with developmental regression. This can be particularly devastating for the families.

They can also have ophthalmologic involvement, such as a cherry red spot, and pulmonary involvement. And the pulmonary involvement can be manifest by aspiration pneumonias and progressive difficulty breathing. This is often the cause of death in these patients. Skeletal manifestations can occur as well. The patient can have osteoporosis and more severe manifestations, such as erosions or even osteolysis, which can occur later in life. GI manifestations can include failure to thrive and the aspirations that we described earlier. The aspirations are believed to be secondary to nodules on the vocal chords, which can give hoarse voice as well. When we describe the pathophysiology, we know that there's mutations in the ASAH1 gene that lead to acid ceramidase deficiency.

This leads to an accumulation of ceramide in the lysosomes. Ceramides are very important for cell signaling, but they can also be

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involved in migration and differentiation, and in our particular case, they can be involved in inflammation. This is a macrophage-driven inflammation that is both local and systemic. So our patient had a homozygous mutation in the ASAH1 gene. This was a c.458A>G mutation. This is something that we've seen in Quebec before, and is part of a Quebec founder mutation, and it results in classical onset Farber Disease in previous cases. Unfortunately, this particular disorder with this particular mutation has led to neurodegeneration and death in the first five years of life. Symptomatic control is difficult, with a poor response to pain medications. So the family had many questions for me at the time of diagnosis, and they were particularly interested if there was any disease-modifying therapies.

At this time, there had been a number of cases that have had stem cell transplantation. Similar to other lysosomal storage diseases, stem cell transplant has been used for patients with neurodegenerative disorders, and I'm going to take a few minutes to describe what's going on here. In this particular case, we have the normal cells replacing the deficient cells, and the normal cells are making the enzyme that will break down the lysosomal accumulation product. We see here in the upper side of this picture that the enzyme is made in the nucleus and gets transported to the lysosomes.

When it's in the lysosomes, it will break down its product. Some of this enzyme also escapes the cell and is taken back up by receptors that exist on the surface of the cell, where it can then be brought back to the lysosome. So indeed, if we do replace some of the patient's deficient cells with some cells that are making this enzyme, we can have cross correction; that is, some of the deficient cells will indeed take up the enzyme by their receptors on the cell surface and bring this enzyme to the lysosome, where they can start to break down the ceramide.

The question is, does this improve outcome in Farber? Well, we can see here that this young girl had a cell stem cell transplant at nine months of age after receiving myeloablative conditioning. She had good chimerism with 100% donor after the transplantation. And we can see here, on the left-hand side, we can see this large nodule on her back, and nodules on her fingers with erythema. At two months post-transplant, these had started to disappear. The erythema was still there, but largely the nodule had decreased.

Significantly as well, as we continued farther down the track, we saw an improvement in her pain, and the anti-inflammatory medications could be discontinued. By 19 months of age, or approximately 10 months post-transplant, we had resolution of the nodules and resolution of all the peripheral nodules, with an improved quality of life. However, when we look at her neurodevelopment, we see that, despite improvement in the peripheral manifestations, we had a gradual decline in development. At 19 months of age, she had good eye contact but she was no longer crawling and had no pincer grasp. She had a decreased response to pin prick, as well, and at 29 months, she had severe developmental delay, with deceleration of head growth and no response to her name.

So, in conclusion, the transplantation has a role to play in Farber Disease. We saw a clear improvement of the peripheral manifestations with improved quality of life, resolution of pain, and much less irritable, but it had little effect on the central nervous system decline. Unfortunately, this young girl died of respiratory failure at the age of 37 months, 28 months after the transplant. This case is quite similar to our experience in the literature, with other cases having resolution of the peripheral manifestations, but no impact on the CNS, and it's quite clear that we need new therapies for Farber Disease. Stem cell transplantation has also demonstrated a proof of concept that replacement of enzyme function can treat symptoms.

This is important, as there's a new enzyme replacement therapy with Aceragen that is in development. The first in human trials are expected to start in 2023. If you have patients that you think may benefit from this trial, you can contact me at the following email. I thank you for your attention today for this short talk and I hope you learned something.

Announcer:
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