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

The Spectrum of Disease Due to the Inherited Deficiency of Acid Ceramidase Activity (ASAH1-Related Disorders)

Announcer:
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Dr. Schuchman:
My name is Ed Schuchman. And I'm a Professor at the Mount Sinai School of Medicine in New York. And it's my pleasure to be with you and to be able to speak to you a little bit about the really remarkable spectrum of disease that can be due to the inherited deficiency of the enzyme acid ceramidase. This is a group of disorders that we refer to now as the ASAH1-related disorders. I'd like to begin with some history. The first case of disseminated lipogranulomatosis was reported by Sidney Farber in a 14-month old infant in 1947.

Several years later, Farber reported three additional cases and identified his now four cases as a new syndrome. Common findings among these patients were dysphonia, enlarged nodules on the joints, hepatomegaly and developmental delay. There was also infiltrated lesions in the skin and subcutaneous tissue that had evidence of lipid storage. Symptoms appeared within the first few months of life and death occurred by 14 months. Years later, in 1967, the accumulating lipid in Farber's original patients as well as several other patients that had been identified was found to be a lipid known as ceramide by Moser and colleagues. And in 1972, the deficient activity of the lysosomal enzyme acid ceramidase was identified in these Farber disease patients.

The schematic at the bottom of this slide shows that acid ceramidase is one of several enzymes that breaks down the lipid ceramide into sphingosine and fatty acid. And in patients with Farber disease, there is an inherited deficiency of this enzyme activity and a buildup of ceramide in cells and tissues. And this is the underlying pathophysiology of this disease. In 1983, Moser and Chen reviewed all the reported cases of Farber disease that were known at that time and there were 27 cases. And they identified a common triad of clinical findings that included painful and deformed joints, subcutaneous nodules, and hoarseness, a hoarse voice. In addition, 10 out of 27 of these cases had impaired psychomotor development. Other findings included respiratory difficulties, hepatomegaly, poor weight gain, and intermittent fevers.

Most cases presented with a very severe early onset phenotype. Although variability in the presentation was observed with onset within the first decade and survival into late adolescence or even adulthood. In 1987, a very important case appeared in the literature which was the first Farber disease case where the patient also had progressive myoclonic seizures. The symptom onset in this patient was at 22 months and death occurred at six years.

So this patient had the common Farber disease triad: painful and deformed joints, subcutaneous nodules, and hoarseness, but lacked hepatomegaly, and as I noted, had progressive myoclonic seizures. The 1990s saw a very rapid and active area of research around acid ceramidase and Farber disease. In 1996, the cDNA and gene sequences encoding human acid ceramidase and this gene is referred to as ASAH1 was isolated. The first ASAH1 mutations were also found causing Farber disease. And using this gene, we had the first production and characterization of the human recombinant acid ceramidase.

In addition, the human gene was used to isolate the mouse gene and this led to the construction of the first knock-out and knock-in mouse models. And with these mouse models in hand, we then could undertake the first proof-of-principle treatment studies in the Farber disease models. And this included enzyme replacement as well as gene therapy studies in the mouse model. In 2012, a very important paper appeared where we saw the first demonstration that a rare form of spinal muscular atrophy that is referred to as SMA-PME was also due to mutations in the ASAH1 gene. So we now had two different diseases that were due to mutations in the same gene. In this paper, there were three unrelated families and six patients reported. Common findings in these patients included muscle weakness, progressive myoclonic seizures, and loss of mobility. Interestingly, there were no skin or joint abnormalities in these patients and no other signs of Farber disease. So these patients were different from that 1987 case that I told you about where the patient presented with the Farber disease phenotype, but also had myoclonic seizures. These patients have as their primary clinical presentation, seizures and muscle weakness, but no signs of Farber disease. In 2018, Medin, Levade and colleagues reported over 200 cases of acid ceramidase deficiency that had appeared in the literature.

This included 158 cases of Farber disease, 23 cases of SMA-PME, and 20 cases that were reported to have an SMA-PME like presentation, somewhat intermediate between Farber and SMA-PME. An extremely wide clinical spectrum was described with the age of onset ranging from about six months to eight years, and the age of death ranging from about 2 1/2 years to 17 years. In addition, we saw two further phenotypes that were associated either with loss of function of the acid ceramidase gene, ASAH1 or mutations in this gene.

And this included phenotypes such as keloid formation and schizophrenia which was found in two different populations, the Han Chinese and Swedish populations. So we now know that acid ceramidase deficiency due to ASAH1 mutations can lead to a very, very wide range of phenotypes and a complex multi-organ system disease. We know of at least two distinct syndromes, Farber Disease and SMA-PME. And, we also know of patients that have intermediate phenotypes between Farber and SMA-PME.

In addition, we have associations of loss of function of this enzyme with schizophrenia and keloids. Furthermore, in many of these patients, we have other organ systems that may be involved, although it's very variable, that includes the ophthalmologic symptoms, respiratory symptoms, GI symptoms, liver disease, bone disease, and others. So an extremely wide range of phenotypes in a very complex multi-organ system disease. So what is responsible for this phenotypic variation? Well, the shorter answer is we really don't know. There's no clear genotype-phenotype correlations that have been found to this at this time. Most of the mutations in Farber disease patients are unique to the individual families, and they're found within the catalytic or beta subunit of the enzyme. In contrast, most of the mutations in SMA-PME patients are found within the non catalytic subunit or the alpha subunit. Very interestingly, there are two mutations that have been found in SMA-PME cases that occur at the same amino acid, amino acid 42, and these account for about half of all the SMA-PME cases.

So this means that this data holds up as more cases identified that perhaps genetic screening could be carried out for this particular form of the Farber disease or the ASAH1-related disease mutations because we have two mutations that predict potentially an SMA-PME phenotype. Now, in terms of residual acid ceramidase activity, there's also no clear relationship between the levels of this residual activity and the phenotype. In part, this is because there are many different laboratories that are performing the enzyme testing and there's no consistent methods that are being used. So we really cannot come up with a level of activity that can predict a given phenotype. So clearly in the future, this is a very important area of future research developing improved methods whether they're genetic or biochemical to predict the phenotypic variability that can occur in this disease. So with that, I'd like to thank you very much and I hope it was an informative presentation. Thank you.

Announcer:
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