PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on the "Inborn errors of metabolism – large molecule disease." These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio version are accessible on iTunes or at www.pedcases.com/podcasts.

Inborn errors of metabolism – Large molecule disease

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January 14, 2016

Intro

Welcome back to podcast number 3 in a series of 3 podcasts around the topic of inborn errors of metabolism. Last time, we spoke about the 'small molecule' diseases. Time for the next category.

My name is Dustin Jacobson, a 2nd year pediatrics resident from the University of Toronto. This podcast was supervised by Dr. Jonathan Kronick, a staff physician in the division of clinical and metabolic genetics at the University of Toronto.

Today, we'll discuss the 'large molecule' diseases. These include glycogen storage, peroxisomal and lysosomal diseases, as well as mucopolysaccharidoses. We'll also talk about the category in general and then place a few prototypes within each category.

Case

But first, let's start with a case. Jonny is a 4-year-old boy who has been referred to you for developmental delay. On history, it appears that Jonny was developing normally from birth to about 1 year of age. From that point, his development has seemed to stagnate, and may in fact have regressed. His parents have also noted changes in his face; from a more round face to a more flat face, with a depressed nasal bridge and bulging forehead. You think this could be the presentation of an inborn error of metabolism.

In general

The large molecule diseases are storage conditions and are classified by lysosomal, peroxisomal or Golgi apparatus disorders and mucopolysaccharidoses. Symptoms tend to be insidious and the conditions present with dementia, epilepsy, movement disorders, gradual blindness and spasticity. Common associations include organomegaly and coarse facial features.

GSDs

Glycogen storage diseases include Von Gierke disease, or GSD1A disease, characterized by a glucose-6-phosphatase defect, and failure to thrive, hepatomegaly, high lactate and fasting hypoglycemia. Another glycogen storage disease is Pompe

disease, or muscle glycogenosis type II. Presentation includes cardiomegaly, hypotonia, and hepatomegaly, and now has enzyme replacement therapy available.

Peroxisomal and lysosomal diseases

Typical peroxisomal and lysosomal diseases include Zellweger syndrome, Gaucher disease, Niemann pick disease and Tay-Sachs disease. In Zellweger syndrome, there is an absence or reduction in peroxisomes. Presentation may resemble trisomy 21. Typical facial features of upslanting palpebral fissures and Brushfield spots are common, along with growth failure and general weakness. These infants rarely live more than a few months. Gaucher disease and Niemann Pick disease are more common in Ashkenazi Jews. Both diseases can present with hepatosplenomegaly. In Gaucher disease, you find thrombocytopenia, anemia, bone pain and lytic lesions in long bones, and diagnosis is aided by finding Gaucher cells in the bone marrow. Treatment is with enzyme replacement therapy and a bone marrow transplant may be effective.

Niemann Pick disease also presents with neurodegeneration and is diagnosed with a white blood cell sphingomyelinase assay, with bone marrow transplant under investigation as a potential treatment. For Gaucher and Niemann Pick disease, a drug called Miglustat has been used to delay the onset of neurologic disease by reducing formation of glucocerebroside, a substance that accumulates and leads to the neurologic sequelae seen in these children.

The last example is Tay-Sachs disease, again more common in Ashkenazi Jews, but also in French Canadian and Cajun populations. Children start missing developmental milestones after 6 months, resulting in seizures, intellectual disability, paralysis and, unfortunately, death by 5 years of age. A cherry red macular spot is common and diagnosis is by enzyme assay. Unfortunately, there is no effective treatment, and prevention is done by screening high-risk populations.

Mucopolysaccharidoses

Last, we get to the mucopolysaccharidoses, or MPS. MPS I, otherwise known as Hurler syndrome, is caused by an alpha-L-iduronidase enzyme deficiency. These infants are normal at birth, but diagnosis occurs at approximately 6-24 months of age when these infants present with hepatosplenomegaly, coarse facial features, corneal clouding, cardiomyopathy, and developmental delay. Bone marrow transplant is the treatment of choice with enzyme replacement used as a temporizing measure. However, death by 10 years of age is common. In MPS II, or Hunter syndrome, features are similar to Hurler syndrome but it is X-linked; however, there is no corneal clouding and there is a slower progression of CNS deterioration. These children typically pass away by 10-15 years of age.

Summary

Let's revisit our case. Jonny's history may be in keeping with an inborn error of metabolism. However, a disease of small molecule metabolism is unlikely, as he has not presented earlier with any acute deteriorations. So, in terms of large molecule

diseases, on exam, his facial features are suspicious for Hunter's or Hurler's syndrome. Now that this is on your radar, more definitive testing and therapy can be sought.

Before we go, we'd like to outline some key take away messages from our 3 podcasts in this series. First, the presentations of IEMs are broad. There is no one presentation of these errors of metabolism; and as such, should be included as a part of a wide array of differential diagnoses. Second, initial investigations along with initial steps in management are important in decreasing likelihood of dramatic and devastating clinical outcomes, along with facilitating diagnosis. With acute presentations this includes possible stopping of all feeds except for glucose, giving supportive care, including ample fluids for those often dehydrated patients, and perhaps most importantly, getting your initial investigations completed while these children are in their catabolic state. Lastly, it's important to have at least 1 or 2 conditions within each category known, as they can present with unique findings, and once remembered, they can help you remember the pathophysiology for the various categories of disease.

References:

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