

PedsCases Podcast Scripts

This is a text version of a podcast from PedsCases.com on the “Inborn errors of metabolism – small 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.pedscases.com/podcasts.

Inborn errors of metabolism – Small molecule disease

Developed by Dr. Dustin Jacobson and Dr. Jonathan Kronick for PedsCases.com

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Intro

Welcome back to podcast number 2 in a series of 3 around the topic of inborn errors of metabolism. If you listened to the first podcast, we discussed inborn errors of metabolism in general, along with some more general supportive measures. Today, we'll discuss more specific diseases.

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Today, we will discuss the ‘small molecule’ diseases. These include amino and organic acidemias, urea cycle disorders, fatty acid oxidation defects, carbohydrate metabolism defects, mitochondrial oxidative phosphorylation disorders, purine and pyrimidine metabolism disorders and pyruvate metabolism disorders. 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 5-year-old boy with known OTC deficiency. He comes in with an upper respiratory tract infection. He is lethargic, and laboratory investigations reveal an elevated ammonia, along with other abnormalities. What are the first steps in management?

In general

‘Small molecule’ diseases often present more acutely, and many lead to acute encephalopathy as they result in a small diffusible metabolite or precursor that accumulate in the brain. Let's talk about some of these disorders.

Aminoacidemias

In the category of amino acidemias, we can place phenylketonuria, or PKU, tyrosinemia, homocystinuria and maple syrup urine disease. PKU is a primary error in phenylalanine hydroxylase, an enzyme that converts phenylalanine to tyrosine. Treatment is lifetime phenylalanine restriction. Most children are normal at birth, but the hallmark is severe intellectual disability if untreated. And, unlike many other ‘small molecule’ diseases,

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PKU does not present acutely, rather, presenting as a chronic developmental disorder if not picked up sooner. They often have a 'mousy' body odour, and may develop a rash similar to eczema. Diagnosis can be suggested by routine neonatal screening but is only confirmed by findings of high phenylalanine levels and typically, low tyrosine levels. Tyrosinemia is distinguished from PKU by high tyrosine levels. Homocystinuria has no neonatal manifestations, but is interesting in that the presentation looks like Marfan's syndrome. Specifically, they can have dislocated ocular lenses, otherwise known as ectopia lentis, long slender extremities, arachnodactyly, scoliosis, pectus excavatum or carinatum and developmental delay. As opposed to Marfan's, the lens dislocation is inferior and inwards in homocystinuria and in Marfan's superior and outwards. However, this aspect is more important for exams than clinically, as it is very difficult to clinically appreciate this difference without specific expertise. The diagnosis of homocystinuria includes elevated total homocysteine and in the most common type, having elevated methionine levels. Treatment includes a diet low in methionine and high vitamin B6 and folate. Maple syrup urine disease is next. Aptly named for the body fluid odour, particularly in cerumen and urine, the disease is caused by a lack of decarboxylation of branch chain amino acids, namely, leucine, isoleucine and valine due to an enzyme deficiency. The incidence is significant in Amish and Mennonite populations and the illness presents in the first days of life with vomiting, lethargy, seizures, coma and without treatment, eventual death. Investigations reveal hypoglycemia, metabolic acidosis and elevated branch chain amino acid levels. Treatment is conservative along with a diet low in branch chain amino acids. A liver transplant is an option for this type of patient.

Organic acidemias

The next category is organic acidemias. These are characterized by presentations, which often include metabolic acidosis, high homocysteine, high ammonia, high ketones and neutropenia. Isovaleric, propionic and methylmalonic acidemia are important to know. In the former, known as IVA, along with the symptoms mentioned previously, the children characteristically have an odour of "sweaty feet" and have elevated IVA in the urine. Treatment includes conservative measures, along with a low protein diet and glycine and carnitine supplements. These supplements encourage urinary clearance of toxic metabolites. Propionic acidemia is similar to IVA, but shows an elevated plasma and urine glycine, and maintenance treatment can include antibiotics, as bacteria in the colon forming propionic acid can contribute to the total load. Methylmalonic acidemia or MMA can be caused by many mechanisms, some of them involving errors in the metabolism of vitamin B12 and as such is often treated with B12 and a low protein diet.

Urea cycle defects

Urea cycle defects are next. Catabolism of amino acids, leads to production of free ammonia, a major neurotoxin in high concentrations. Normally, the urea cycle detoxifies ammonia to urea. Without this process occurring properly, these children become symptomatic within a few days of protein feeding with symptoms consisting of poor feeding, vomiting, tachypnea, seizures, coma and without treatment, death. Investigations reveal low urea, normal pH, and transaminitis and lastly, plasma amino acids may be abnormal. The specific breakdown of plasma amino acids can classify the

urea cycle defects. In these conditions, hyperammonemia is the hallmark, and long-term treatment includes protein restriction and nitrogen scavenging medications. Along with this treatment, avoiding catabolic states is paramount. A prototype of a urea cycle disorder includes ornithine transcarbamylase, or OTC deficiency the only X-linked urea cycle defect. It is the most common defect, and is characterized by elevated glutamine and alanine and low citrulline and arginine levels. Diagnosis also includes urinary orotic acid, and gene sequencing for the OTC gene. A liver transplant is curative in this condition.

FAO defects

Fatty acid oxidation defects lead to hypoketotic hypoglycemia, elevated liver enzymes and fatty infiltration of the liver. Treatment includes avoiding fasting and providing calories with stress that is low in fat and high in carbohydrates. Cornstarch therapy is occasionally used during overnight fasting in patients with particularly severe disorders. Diagnosis is aided by checking the urine for organic acids and most importantly, a plasma acylcarnitine profile. Prototypes for these conditions include MCAD, VLCAD and LCHAD deficiency. When MCAD was discovered, it was found to be a cause of sudden infant death syndrome. Treatment includes avoiding specific length chain fatty acids and triglycerides.

Carbohydrate metabolism defects

Some more common carbohydrate metabolism defects include galactosemia and hereditary fructose intolerance. In the former, presentation occurs typically on day 4 of life, with jaundice, hepatosplenomegaly, vomiting, hypoglycemia, lethargy & seizures. These infants are at an increased risk for E. coli sepsis and diagnosis is aided by looking in the urine for reducing substances. Treatment involves avoiding lactose (giving rise to galactose in vivo), which includes avoiding breast milk and most formulas and milk, which all have lactose as the primary sugar. Hereditary fructose intolerance reveals itself once fructose or sucrose is ingested, and presents with jaundice, hepatomegaly, vomiting, lethargy and seizures. Investigations show features of liver disease, and the urine is positive for reducing substances. Treatment includes diet restriction of fructose, sucrose and sorbitol.

Mitochondrial disorders

Mitochondrial oxidative phosphorylation disorders are an evolving category, and manifestations are more common in tissues with a high-energy demand. Symptoms such as seizures, hypotonia, ophthalmoplegia, stroke-like episodes, muscle weakness and cardiomyopathy are common. These children often present with a profound lactic acidosis. An example of this disorder is MELAS, or mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes syndrome. These children suffer from repeated episodes of 'chemical strokes', myopathy, lactic acidosis and progressive neurodegenerative disease. It is important to remember that these mitochondrial disorders can be inherited maternally or more commonly in a Mendelian fashion, so the family history can be particularly helpful in suggesting a mitochondrial disorder.

Purine and pyrimidine metabolism disorders

Purine and pyrimidine metabolism disorders are most notably typified by Lesch-Nyhan syndrome. This is an x-linked recessive disorder caused by a deficiency in the HPRT enzyme, resulting in increased purine accumulation. It usually manifests between 3-12 months of age, with a xanthine precipitates in the urine, which are orange in colour. Other findings include intellectual disability, symptoms of gout, involuntary movements, cerebral palsy and most typically asked for on exams, self-mutilating behaviour.

Pyruvate metabolism disorders

The last small molecule disease category is pyruvate metabolism disorders and includes pyruvate dehydrogenase deficiency, the enzyme responsible for the generation of acetyl CoA from pyruvate for the Krebs cycle. It manifests as lactic acidosis with CNS malformations and diagnosis is aided by enzyme analysis of skin fibroblasts and DNA testing. Treatment with a low carbohydrate or ketogenic diet is beneficial for some patients.

Summary

Let's revisit our case. OTC deficiency is a urea cycle defect, and presents with elevated levels of ammonia, particularly in the face of stresses, which in our case includes an infectious source. In terms of acute management, remember to stop all protein, the source of ammonia. Next, provide supportive care, including IV fluids with high dextrose content (either 10 or 12.5%). Usually one should supplement 1.5x their maintenance requirement, after any resuscitation efforts. Last, in this case, some nitrogen scavenging therapies may be helpful in decreasing ammonia levels, as this child awaits more definitive therapy such as possible dialysis.

The next large categories of inborn errors of metabolism are the 'large molecule' diseases. For more information about this category, please see our final podcast in this series.

References:

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