PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on the "Inborn errors of metabolism – general approach." 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 – General approach

Developed by Dr. Dustin Jacobson and Dr. Jonathan Kronick for PedsCases.com
January 14, 2016

Intro

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 will discuss an approach to inborn errors of metabolism. First, we will examine the epidemiology and pathophysiology of inborn errors of metabolism and their various presentations. Next, we will talk about their general presentations and how they vary by age group. After that we will talk about general investigations and treatment pertinent to inborn errors of metabolism. Last, we will discuss developmental delay, as an entity that may be caused by inborn errors of metabolism.

Case

But first, let's start with a case. Jonny is a 2-week-old infant who comes into the ER with parental concerns around lethargy, decreased ability to feed and irritability. With these vague symptoms, should we consider an inborn error of metabolism?

In General

Inborn errors of metabolism, hereafter referred to as IEMs, are a rare diagnosis, but often under recognized. They represent at least 1 in 2000 to 3000 births. To put this in context, the prevalence is similar to cystic fibrosis; however, the latter is much more recognized. The most common subtype of inborn errors of metabolism probably includes the rising known prevalence of mitochondrial diseases. We will speak about this category later in our podcast series.

The pathophysiology of IEMs generally exist when either toxic substrates or metabolites accumulate, there are deficient products of metabolism, or a combination of the two. Other more rare mechanisms include congenital disorders of glycosylation, membrane or organelle transport or synthesis disorders, and other more rare mechanisms of cellular dysfunction.

Inborn errors are sometimes picked up on the provincial newborn screen. It is important to note though that similar to other conditions screened for, the newborn screen is not a

diagnostic tool. Also, milder forms of these diseases may be missed on the newborn screen and many IEMs are not included in the screening panels.

Presentation

Infants present with a variety of symptoms when they are picked up symptomatically. Various signs and symptoms include hypoglycemia and resultant irritability and jitteriness, jaundice and other signs of liver disease, such as encephalopathy, hepatomegaly or splenomegaly, cataracts, seizures, sepsis, cardiomyopathies, characteristic odours and failure to thrive. Clearly, the diagnosis is difficult because of these broad degrees of presentation, and therefore one must keep a high index of suspicion.

The next division of presentation is in the childhood age group. This is the most common age group that present with IEMs and they present similarly to neonates. Clinical clues from the history and family history are often very telling. First, presentations are often triggered by stress. This can include events such as illness, fasting or a dietary change such as the introduction of high protein food, or some other stressor. There may be a family history significant for consanguinity, typical inheritance patterns (for example, maternal inheritance or x-linked inheritance) or a typical ethnicity for various conditions.

Investigations

Routine investigations may reveal clues to the diagnosis. Typical findings can include hypoglycemia with high or low ketones, anion gap metabolic acidosis, respiratory alkalosis, electrolyte disturbances and elevated lactate. With these routine investigations, one can move into more primary investigations for IEMs. These include investigations on the urine and blood. In the urine, one should test for organic and amino acids, reducing substances and oligosaccharides. In the blood, one should test for glucose, electrolytes, ammonia, lactate, urate, amino acids, carnitine and an acylcarnitine profile. Importantly, samples must be obtained quickly, because with correction of the disturbance as part of the initial management, laboratory abnormalities may be masked. Secondary investigations are directed by history and physical, along with your initial primary investigations, but these are beyond the scope of this podcast.

Treatment

Initial treatment for IEMs is based on treating the underlying triggering disorder if it is known, general supportive care, and decreasing toxic substrates, metabolites and/or replacing deficient products. Breaking this down further, supportive care is often life saving, particularly giving ample fluids and calories. These children are often low in their volume status and replacement is necessary; with careful attention to the risk of volume overload if overly corrected. Acutely ill patients are at significant risk for developing cerebral edema. Although we think of fluid as the most important therapy for acute decompensations, in fact, in most cases, calories are more important in an attempt to decrease catabolism, which is often the major component of metabolic decompensation.

In terms of more specific therapy to decrease toxic substrates or metabolites, decreasing catabolism is done by controlling fever and again, providing calories. These calories are best given as glucose to ensure the most basic utilization can take place, especially when the error is unknown. Eliminating exogenous substrates is done by eliminating protein from the diet. Lastly, reducing endogenous toxic substrates is done when this substrate is known. Specific medications have been developed to reduce these substrates. For example, to remove ammonia, medications such as phenylacetate, sodium benzoate and arginine are given to enhance elimination. A more general way to go about eliminating exogenous substrates include hemofiltration or dialysis, administration of cofactors and vitamins, or enhancing in vivo enzyme activity. Future therapies may include specific cofactor or enzyme administration, gene therapy, and organ or tissue transplantation (i.e. liver transplantation and bone marrow transplantation) for selected disorders.

Another important discussion with the patient's family includes what is best referred to as a metabolic autopsy. If the patient unfortunately passes away, it is important to collect biological samples to allow subsequent diagnosis for the benefit to the family and future children. Post-mortem investigations can be done on the blood and urine, along with tissue examination, from which biochemical evidence and DNA may be used for diagnosis.

IEMs & Developmental Delay

Another important category of presentation and investigation for IEMs exists in the realm of developmental delay. Developmental delay is a common presentation for IEMs. Very mild delays, such as delays in only one category of development are not typical for a genetic disorder. Rather, global developmental delay is the typical presentation. A family history of consanguinity, or typical inheritance patterns as mentioned previously may provide clues to the diagnosis. However, these diagnoses may be sporadic in nature and importantly, initial management is not acute. Rather, the diagnosis is most important, and as such, investigations are the priority. Investigations really should be guided by history and physical findings.

General investigations can be included; such as a microarray, which is positive for an underlying diagnosis in approximately 14% of children with severe global developmental delay. This number will likely increase in the future as more genetic conditions are found. Another important investigation is for fragile X syndrome. Initial metabolic investigations yield a diagnosis in approximately 1% of children with severe developmental delay. These investigations can include things like plasma and urine amino acids, acylcarnitine profiles, plasma homocysteine, urine organic acids, urine creatine and guanidinoacetate as well as ammonia, lactate, urate and glucose.

Summary

Finally, let's come back to the case. Jonny has symptoms of lethargy and irritability; both of which are suspicious for an IEM, amongst various, more common, other causes. However, because it's on our differential, in terms of management for this patient, as a first step, it is important to stop any protein feeds. Next, we would elect to start 10%

dextrose containing IV fluid at 1.5x maintenance. However, as mentioned previously, before this dextrose is administered, it is important to draw your investigations that are pertinent in screening for potential IEMs. Let's go over them again. We would order in this case, blood gas, electrolytes, glucose, ketones, lactate, ammonia, urate, amino acids, carnitine and acylcarnitines. In the urine, we would also add organic and amino acids, reducing substances and oligosaccharides.

Moving onto specific diseases and their presentations, please see our upcoming podcasts.

References:

1. Pediatr Rev. 2016 Jan;37(1):3-17. doi: 10.1542/pir.2014-0122. **Inborn Errors of Metabolism (Metabolic Disorders).** Rice GM, Steiner RD.
2. Pediatr Rev. 2009 Apr;30(4):131-7; quiz 137-8. doi: 10.1542/pir.30-4-131. **Inborn errors of metabolism: part 1: overview.** Levy PA.
3. Pediatr Rev. 2009 Apr;30(4):e22-8. doi: 10.1542/pir.30-4-e22. **Inborn errors of metabolism: part 2: specific disorders.** Levy PA.