PedsCases Podcast Scripts

This podcast can be accessed at www.pedscases.com, Apple Podcasts, Spotify, or your favourite podcasting app.

Maple Syrup Urine Disease

Developed by Angela Messer and Dr. Shailly Jain for PedsCases.com
Sept 4, 2022

Introduction:

Hi there, my name is Angela Messer, and I am a fourth- year medical student at the University of Alberta. This PedsCases podcast will provide listeners with an understanding of Maple Syrup Urine Disease, its clinical signs and symptoms, and management. This podcast was developed in collaboration with Dr. Shailly Jain, who is an Associate Professor in the Department of Medical Genetics at the University of Alberta.

Learning Objectives:

At the end of this podcast, you should be able to:

1. Discuss the epidemiology, genetics, and pathophysiology of Maple Syrup Urine Disease (MSUD)
2. Define the different types of MSUD (classic, intermittent, intermediate, thiamine-responsive, E3- deficient)
3. Recognize the initial presentation, differential diagnosis, and investigations required to diagnose MSUD
4. Outline the short- term and long- term management of MSUD in children

Case Presentation:

Let's begin with a clinical vignette. You are a third- year medical student on your core pediatrics rotation. You are asked by your preceptor to see a new consult in the emergency department: a 4-day old term infant, Hunter, presenting with increasing irritability, vomiting, and new- onset seizures. On history obtained from his parents, you determine that he was born at 39 weeks and 3 days via spontaneous vaginal delivery and weighed approximately 3200g. His APGAR scores were 7 and 9 and he did not require any resuscitation. He and his mother were discharged the following day without complication. Since coming home, his mother has noticed that Hunter is not eating as well as he initially was, largely because he is so lethargic. When he is alert and awake, he is extremely fussy and "inconsolable," mom states. This morning, when she went to pick him up from his crib, she noticed that he was twitching his right arm, and soon his

entire body began to shake uncontrollably for a minute or two. She called 911 and he was brought into the ED promptly for further work- up.

Epidemiology, Genetics, and Pathophysiology:
Let's now focus back on our topic of discussion today, Maple Syrup Urine Disease. MSUD is a rare metabolic disorder with an incidence rate of around 1 per every 185, 000 infants born in Canada. It is an autosomal recessive inherited condition, one of the so- called amino acid disorders. These are a group of heritable metabolic disorders in which certain amino acids cannot be metabolized or broken down into their component parts. As a result, toxic metabolites will accrue over time causing a wide array of short-term and long- term health issues. In MSUD, these metabolites are excreted into the urine, producing a characteristic sweet odor for which the disease got its namesake. The disease can involve any ethnicity; however, it is more common in communities where there are higher rates of consanguinity.

MSUD manifests as a defect in the ability to breakdown branched chain amino acids, i.e., leucine, isoleucine, and valine. The disorder is also known as branched- chain alpha- keto acid dehydrogenase deficiency. The causes of MSUD are pathogenic variants in the genes that code for an enzyme complex known as branched- chain alpha- keto acid dehydrogenase complex (BCKDC), which catabolizes the branched chain amino acids into breakdown products. Deficiency in BCKDC leads to elevations in leucine, isoleucine and valine. Elevations in leucine and its metabolites result in the symptoms seen in MSUD. Additionally, elevations in leucine and its derivative α-Ketoisocaproic acid, can disrupt metabolism of other amino acids and neurotransmitters, such as glutamate, GABA, glutamine, alanine, and aspartate. α-Ketoisocaproic acid can also cause inhibition of oxidative phosphorylation, inducing cerebral metabolic acidosis. These are thought to be the main precipitants of the presenting encephalopathy and eventual cerebral edema that is characteristic of the disease.

Types of Maple Syrup Urine Disease:
There are five main subtypes of MSUD. These are defined according to the severity of the clinical presentation. As follows:

- **Classic MSUD** is considered the most severe form of this disease. These patients have between 0 to 2% of enzyme activity as compared to controls. Children present in the first few days of life with poor feeding, vomiting, lethargy, seizures, and eventually, coma. They may develop cerebral edema and require admission to the intensive care unit for management. Metabolic derangements include varying degrees of ketoacidosis and hypoglycemia (which once corrected, does not result in improvement in seizure activity).

- **Intermediate MSUD** is a milder form in which affected individuals may present later in early childhood with insidious signs of CNS involvement, such as varied degree of intellectual disability and seizure. Their dehydrogenase activity is higher than observed in classic MSUD. These children may become quite ill with

the signs and symptoms of classic MSUD in the case of intercurrent illness, where metabolic decompensation can become more prominent.

- **Intermittent MSUD** is a subtype of MSUD in which children present with signs and symptoms of maple syrup urine disease in the event of catabolic stressors, such as illness or surgery. These children are often otherwise healthy. Thus, there is often a delay in diagnosis in these children. Enzymatic activity in these patients can reach up to 40%.

- **Thiamine- responsive MSUD** is a rare form of the disease in which children may respond in part to thiamine supplementation. Thiamine is a cofactor for BCKDC. Thiamine supplementation in certain pathogenic variants may increase enzyme activity. Similar to intermittent MSUD, enzymatic activity in these patients can reach up to 40%.

- **E3-deficient MSUD** is another rare form of MSUD involving variants in what is known as the E3 component of the enzyme complex. These patients may present similarly to those with intermediate MSUD; however, they typically present in the newborn period with lactic acidosis.

In our discussion today, we will be focusing mainly on classic MSUD, as this is the most common form of the disorder. It is important to keep in mind, however, that the other subtypes may also present similarly to classic MSUD.

Case Presentation Continued:
Let's return now to our case. After obtaining a history from Hunter's mother, you perform a physical exam. Hunter's vitals are as follows: blood pressure is 70/45mmHg, heart rate is 145bpm (awake), respiratory rate is 55rpm, O2 saturation is 96% on room air, and temperature is 36.6°C. Notably on exam Hunter is quite hypertonic and rigid. You note that he smells oddly sweet, especially when you remove his diaper to examine his genitourinary region.

Initial Presentation, Differential Diagnosis, and Investigations in the Diagnosis of MSUD:
The presentation of classic MSUD follows a predictable timeline. Importantly, babies are asymptomatic at birth. Within the first 24-72h of life, infants will develop poor feeding, vomiting, irritability, and increasing lethargy. By around days 4 to 6, infants will have signs and symptoms of worsening encephalopathy, such as extreme lethargy, apneas, dystonias, opisthotonos, and reflexive "boxing" and "bicycling" movements of the upper and lower limbs, respectively. Around one week to ten days of life, infants will become critically ill, with cerebral edema, central respiratory failure, coma, and ultimately, death, becoming imminent.

In Alberta, routine screening for MSUD is included in the newborn metabolic screen sent 24 hours after birth. Despite this, babies may re- present following their initial discharge before these results are reported. It is thus important to keep this diagnosis in

the differential of an unwell infant presenting in the first few days of life. Other diagnoses on the differential diagnosis of the encephalopathic neonate include sepsis, meningoencephalitis, status epilepticus, birth asphyxia, hypoglycemia, kernicterus, and other inborn errors of metabolism, among others. Of note, sepsis must be ruled out in the unwell neonate as this can have fatal consequences if not detected and treated early. Additionally, meningitis must also be considered, as the presentation in neonates may be subtle and non-specific, for example, vomiting and lethargy in the absence of classic findings.

For a diagnosis of maple syrup urine disease, confirmatory lab testing must be performed. Specialized metabolic tests known as serum amino acid analysis, will reveal marked elevations in the branched chain amino acids and alloisoleucine, as well as decreased levels of alanine. Although there are additional tests that may also be necessary to rule out other metabolic disorders, it is the classic serum elevation in BCAAs with alloisoleucine that ultimately confirms MSUD.

Case Presentation Continued:
And now back to our case. After discussion with your preceptor, you admit the patient and order a full septic work- up, including a lumbar puncture, to rule out sepsis and meningitis. Hunter is started on empiric antimicrobial coverage and fluid resuscitation is initiated. Your preceptor also recommends an urgent consult to the pediatric metabolic team, as she is suspicious of MSUD based on Hunter's presentation and the peculiar odor of his urine. His preliminary diagnosis comes back shortly, as you notice that his newborn metabolic screen results come back later that afternoon flagged as 'abnormal.' The appropriate investigations are then sent off and Hunter is treated for presumptive MSUD as you await confirmatory results.

Short- term and Long- term Management of Patients with MSUD
Short- term management of a patient in acute metabolic decompensation involves aggressive rehydration and the removal of BCAAs and metabolites from the body. Often hydration alone is not enough, given poor renal clearance of leucine. Thus, children in acute crisis may require hemodialysis or exchange transfusion if critically ill. Additionally, management of the catabolic state is also critical to help with reduction in the branched chain amino acids; protein synthesis will be stimulated, and as the BCAAs are incorporated into new proteins, they will be eliminated from the bloodstream. One of the more dangerous sequelae of acute metabolic decompensation is that of cerebral edema, which if present, may be managed using conventional osmotic therapies (such as hypertonic saline, mannitol).

Recall that leucine is believed to be the culprit behind MSUD- induced encephalopathy. Although somewhat counterintuitive, careful administration of isoleucine and valine will allow for competition with leucine for the LNAA transporter at the blood-brain barrier. This will effectively reduce the level of leucine allowed into the central nervous system.

Long- term management of patients with MSUD involves dietary modification to ensure low consumption of BCAAs. These are essential amino acids that cannot be made

endogenously, thus levels can only be influenced by exogenous sources and during catabolic events such as illness, infection, or even strenuous exercise. As such, patients must receive minimal amounts of isoleucine, valine, and leucine to ensure adequate levels are maintained for protein synthesis. Meticulous monitoring of plasma amino acid levels is necessary to ensure that MSUD patients are not becoming deficient of essential amino acids over time.

Another treatment modality that has emerged is that of liver transplantation in select patients. Around 10% of BCKDC enzymatic activity occurs in the liver, and when healthy donor hepatocytes replace the recipient's hepatocytes with MSUD mutation, they can take on the role of metabolizing BCAAs throughout the body. While these patients will not be entirely cured of their disease with liver transplant, it greatly reduces disease severity and there is evidence to suggest it may be neuroprotective over time. Despite these benefits, liver transplantation is only recommended in certain candidates. Just as with any other solid organ transplant, liver transplant comes with great risk and involves chronic immunosuppression and lifelong management to prevent rejection of the donor organ.

Overall, the prognosis in children with MSUD varies accordingly with the severity of their illness and how frequently they decompensate into metabolic crisis. Any episode of severe metabolic deterioration can potentially have lasting neurologic and cognitive effects and drastically change patient outcomes.

Conclusion

Now that we have discussed the epidemiology, pathophysiology, initial presentation, management, and prognoses of patients with maple syrup urine disease, let's review the pertinent take-home points:

1. Maple Syrup Urine Disease is a rare condition, affecting around 1 per every 185, 000 infants. MSUD is one of the inborn errors of metabolism, resulting from genetic variants in the DNA encoding the enzyme complex that breaks down branched chain amino acids (leucine, valine, and isoleucine).
2. MSUD manifests as inability to properly breakdown and metabolize BCAAs. Depending on the subtype- classic, intermediate, intermittent, thiamine-responsive, and E3-deficient- the timeline of presentation will vary. Classic MSUD is the most severe form of the disease and manifests in the early days of infancy as poor feeding, lethargy, irritability, and progressive deterioration into seizures, dystonic movements, abnormal posturing, coma, and eventually, death.
3. Early management of patients in acute metabolic crisis involves fluid resuscitation and elimination of leucine from the body- often via hemodialysis or even exchange transfusion. Long- term management involves strict dietary control of BCAA consumption, with careful titration of levels to age- appropriate norms, and in select patients, liver transplantation.
4. Prognosis of maple syrup urine disease improves with early detection and treatment, however, remains guarded. Neurological sequelae and developmental delay are common long- term complications.

Developed by Angela Messer and Dr. Shailly Jain for PedsCases.com.
Dec 6, 2021.

Thank you again for listening to this podcast on Maple Syrup Urine Disease.

References

1. Nyhan, W.L., Rice- Kelts, M., Klein, J., et al. Treatment of the Acute Crisis in Maple Syrup Urine Disease. *Archives of Pediatrics and Adolescent Medicine.* 1998; 152(6):593-598. doi:10.1001/archpedi.152.6.593

2. Bodamer, O.A. Overview of Maple Syrup Urine Disease. UpToDate. https://www.uptodate.com/contents/overview-of-maple-syrup-urine-disease?search=maple%20syrup%20urine%20disease&source=search_result&selectedTitle=1~23&usage_type=default&display_rank=1#H16. Published 2021. Accessed Oct. 5, 2021.

3. Kliegman, R.M., St. Geme, J.W., Blum, N.J., Shah, S.S., Tasker, R.C., & Wilson, K.M. *Nelson Textbook of Pediatrics.* Edition 21. Philadelphia, PA: Elsevier: 2020. Pp. 3188- 3190.

4. Mazariegos, G.V., Morton, H.D., Sindhi, R., Soltys, K., Nayyar, N., Bond, G., Shellmer, D., Schneider, B., Vockley, J., & Strauss, K.A. Liver Transplantation for Classical Maple Syrup Disease: Long-Term Follow-Up in 37 Patients and Comparative United Network for Organ Sharing Experience. *Journal of Pediatrics.* 2012; 160(1): 116-21.e1. doi:10.1016/j.jpeds.2011.06.033

Developed by Angela Messer and Dr. Shailly Jain for PedsCases.com.
Dec 6, 2021.