

Metabolic Mayhem:

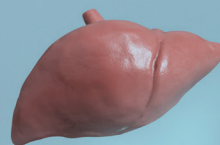
Wesley Wrestles with an Organic Acidemia

by

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Part I – Unexpected Challenges

Section A – Delivery

Kat excitedly packed her hospital bag for the short stay that would follow the birth of her son. The pregnancy had progressed smoothly, and she was looking forward to holding her baby. Right on time, she went into labor and was taken to the community hospital. Unfortunately, labor did not progress as expected, and Kat had an emergency caesarean section on Friday night, right before midnight. It was worth it though: Wesley was perfect! He was a beautiful baby with normal responses for all of the items on the newborn health check.

Because of the late-night C-section, Kat was not discharged from the hospital 24 hours after giving birth, as she originally expected. Since her discharge date was moved to Monday, she spent the weekend resting and practicing breast feeding Wesley. Sunday night, a few hours before midnight, she noticed that Wesley's breathing was labored with forceful inhalations that almost seemed liked violent hiccups. He also became limp and unresponsive. The nurse immediately called the medical resident, who ordered a series of blood and urine tests. They also began the process of transferring Wesley to the neonatal intensive care unit (NICU) at the regional medical center across town. Kat watched helplessly as her baby was transferred to a hastily summoned ambulance. In fact, she was close to hysterics; she was unable to accompany Wesley to the other hospital since she was still a postpartum patient at the community hospital, recovering from major surgery.

At the regional medical center, the NICU staff worked quickly to try and determine what caused Wesley's dramatically changed condition. The combined test results from both hospitals are shown below.

Table 1. Wesley's clinical test results few days after birth.

	<i>Ammonia, NH₃</i> ($\mu\text{g} / \text{dL}$) (serum)	<i>Bicarbonate Ion, HCO₃⁻</i> (mEq / L) (serum)	<i>pH</i> (serum)	* <i>Organic Acids</i> (urine)
Normal	† 170 – 341	‡ 22 – 26	7.35 – 7.45	low levels
Wesley	1587	8	6.9	§ Elevated levels of several organic acids, including 3-hydroxypropionate, propionylcarnitine, propionylglycine, methylcitrate, and lactic acid.

* Organic acids are also present in the serum, but Wesley's urine was tested.
 † Colombo et al., 1984.
 ‡ Arias-Oliveras, 2016.
 § Di Donato et al., 1984; Fraser & Venditti, 2016.

Questions

1. How is Wesley's blood chemistry abnormal?
2. Why does Wesley develop labored breathing and become listless? Explain your answer in terms of the acid/base balance in the blood.
3. Speculate on the reason why these organic acids were found in elevated amounts in Wesley's urine.
 - Consider the common functional group in 3-hydroxypropionate, propionylcarnitine, and propionylglycine.
 - Consider the lactic acid component separately from the other organic acids.

Section B – Dialysis

The most critical aspect of Wesley's blood chemistry was his ammonia level. It was imperative that excess ammonia be removed from his blood as soon as possible. There happened to be a dialysis center across the street from the regional medical center. Early Monday morning, the dialysis technicians worked to get Wesley attached to the dialysis machine. It was challenging to get even the smallest dialysis needles into his tiny veins. Success! He became the youngest patient to undergo dialysis in the center.

Questions

4. How does Wesley's biochemical situation lead to excess ammonia in his blood?
5. Excess ammonia is toxic to the brain. Speculate on why this is so. (Refer to Braissant et al., 2013.)

Section C – Intravenous Solutions

It was hoped that his ammonia levels would normalize after dialysis, but unfortunately this did not happen. On Tuesday, Wesley was given several intravenous solutions, each with a dedicated intravenous line:

- sodium phenylacetate and sodium benzoate; phenylacetate binds to glutamate and benzoate binds to glycine;
- bicarbonate ion;
- carnitine; and
- a drug to reduce his elevated blood pressure.

Wesley was also placed on oxygen and fitted with a gastric feeding tube. The feeding tube snaking through his nose, sinuses, and down his throat must have been uncomfortable because he pulled it out more than once over the next several days. While his spunk greatly cheered the NICU staff, he was nevertheless a very sick baby. Kat, still recovering from her C-section, was reeling from the reality that her son was not the perfectly healthy baby he seemed just a few days earlier.

Questions

6. Consider Wesley's clinical test results. How does the administration of sodium phenylacetate with sodium benzoate, bicarbonate ion, and carnitine alleviate some of Wesley's acute biochemical problems?

7. Untreated high blood pressure can result in damage to the kidneys and the brain. Speculate on how damage to Wesley's kidneys and brain could exacerbate his health crisis.

Section E – Mutations

PA is an autosomal recessive disease affecting fewer than 0.001% of infants born in the United States. Wesley is heterozygous for two different mutations in PCCA, as shown in Table 2.

Table 2. Propionyl CoA carboxylase genes.

	<i>Alpha (A) subunit</i>	<i>Beta (B) subunit</i>
*Chromosome location	13q32.3	3q22.3
Protein MW	72–80 kDa	58 kDa
# Amino acids	681–729 (three normal variants, formed by alternative splicing)	539
Wesley's mutation #1	Exon 10 missense mutation, E261G	
Wesley's mutation #2	Intron 23 polymorphism linked to PA	

*OMIM #606054

It is not known if both of Wesley's mutations in his PCCA gene are on the same or different alleles of chromosome 13. In other words, doctors did not determine if his maternal and paternal alleles each carry one of the mutations, or if both mutations are on one allele.

Questions

- Wesley's first mutation in Exon 10 involves the substitution of glycine (G) at position 261 in place of the original glutamate (E). How does the lack of glutamate in this position affect the structure and function of PCC?
- Mutations within intron sequences are frequently linked to changes in RNA splicing. How does Wesley's second mutation affect the structure and function of PCC?
- Develop a plausible PA screening test for newborn infants. Can this screening test be successfully implemented throughout the world in every type of birth setting? Explain.

Section F – Daily Regimen

Wesley's metabolic fragility was complicated by a cerebral vascular accident (CVA, also called a stroke) before he was a week old, likely caused by high ammonia levels. Because of the constant metabolic damage caused by PA, he was at higher risk for additional strokes or seizures, which can cause cognitive impairment. His doctors modified their expectations for his long-term recovery and ability to reach pediatric developmental milestones. They shared with Kat that he might never crawl or walk. He might never learn to speak or use a pencil or even feed himself. Wesley's medical team told Kat that his best hope for improved future health was a liver transplant within the next year or so. A few months after Wesley's first birthday, Kat received the long-awaited phone call: a strongly matched liver was available! He was flown immediately to the transplant center and prepped for surgery. Kat accompanied him on the flight, but a few members of her immediate family had to drive to the medical center, bringing clothes and supplies for their expected extended stay.

Wesley was closely monitored for several weeks since tissue rejection can begin immediately following transplant surgery. He also faced a couple of years of follow-up surgeries. One was expected: the donor liver was too large for his abdomen, so his abdominal wall could not be fully closed until he had grown significantly. Other potential surgeries were common for liver transplant recipients. For example, he might need to undergo liver biopsy procedures to determine if tissue rejection had begun or have surgery to correct problems with the transplanted bile ducts.

Following his liver transplant, Wesley needed to maintain his low-protein diet. In addition, his daily regimen included specific nutritional supplements and several pharmaceutical agents.

Question

14. Use any reputable pharmacology website to investigate the general biochemical role for each of the following components in Wesley's daily regimen:
- Amlodipine
 - Benadryl
 - Clonidine
 - Ergocalciferol
 - Ferrous sulfate
 - Fludrocortisone
 - Lansoprazole
 - Levocarnitine
 - Ursodiol

Section G – Development

Despite his metabolic fragility, Wesley has continued to grow and develop into a lively preschool-aged boy. He continues to need a feeding tube, since an inexplicable side effect of his disease is the inability to tolerate the feel of food in his mouth. He has constant diarrhea. He does not speak but he does squeal with delight and cry from frustration. He is learning sign language and he responds to Kat's requests and directions. He cannot (yet!) hold a pencil but he runs, jumps, and will sit still for a favorite video. He loves music, is fascinated with shadows, and enjoys playing in water. In short, he is in many ways a typical preschooler who happens to be living with propionic acidemia.

Part II – Liver Transplant

Section A – Reducing Metabolic Damage

Wesley’s metabolic fragility was complicated by a cerebral vascular accident (CVA, also called a stroke) before he was a week old, likely caused by high ammonia levels. Because of the constant metabolic damage caused by PA, he was at higher risk for additional strokes or seizures, which can cause cognitive impairment. His doctors modified their expectations for his long-term recovery and ability to reach pediatric developmental milestones. They shared with Kat that he might never crawl or walk. He might never learn to speak or use a pencil or even feed himself. Wesley’s medical team told Kat that his best hope for improved future health was a liver transplant within the next year or so. However, they stressed that a liver transplant would not cure him.

Question

1. How would a liver transplant help Wesley? Why would it not cure him?

Section B – Organ Donation

Before he could be placed on the transplant recipient list, Wesley needed heart surgery to address a different birth defect that was unrelated to PA. Correcting this defect would ensure that his heart was strong enough to withstand a future liver transplant. Kat lived about three hours by car from a specialty medical center that performed pediatric organ transplants but not pediatric cardiac surgery. She had family near this medical center who were willing to let her stay with them during Wesley’s transplant surgery and follow-up appointments. Of course, he would first need cardiac surgery somewhere else. Kat lived about six hours by car from a specialty medical center that performed both types of pediatric surgeries. While this was more convenient for Wesley because it consolidated his complicated care, Kat would have to find accommodations for several extended stays in the area over the next couple of years.

Wesley was placed on the liver transplant list immediately after recovering from his heart surgery. Kat chose to wait for a deceased donor. Over the course of several months, she received a few calls from the transplant center regarding possible matches but none of those livers were ultimately approved for Wesley. As he neared his first birthday still waiting for a liver, Kat decided to expand the donor eligibility to include living donors. She was also asked to consider whether Wesley should receive the usual vaccination series given to one-year old children. Getting the vaccines would remove him from the transplant list for one month; however, after his transplant, he would be limited in the type of vaccinations that he could get.

Questions

2. What are the relevant issues pertaining to a deceased organ donor versus a living donor?
3. Why does Wesley’s need for a liver transplant affect his eligibility for vaccinations?

Section C – The Match

A few months after Wesley's first birthday, Kat finally received the long-awaited phone call from the specialty medical center: a strongly matched liver was available! He was flown immediately to the transplant center and prepped for surgery. Kat accompanied him on the flight, but a few members of her immediate family had to drive to the medical center, bringing clothes and supplies for their expected extended stay.

Wesley was closely monitored for several weeks since tissue rejection can begin immediately following transplant surgery. He also faced a couple of years of follow-up surgeries. One was expected: the donor liver was too large for his abdomen, so his abdominal wall could not be fully closed until he had grown significantly. Other potential surgeries were common for liver transplant recipients. For example, he might need to undergo liver biopsy procedures to determine if tissue rejection had begun, or have surgery to correct problems with the transplanted bile ducts.

Questions

4. How are an organ donor and organ recipient “matched”?

5. How does tissue rejection (also called host-versus-graft disease) occur?

6. Why is it biochemically important to have functioning bile ducts?

Section D – Daily Regimen

Following his liver transplant, Wesley needed to maintain his low-protein diet. In addition, his daily regimen included specific nutritional supplements and several pharmaceutical agents.

Question

7. Use any reputable pharmacology website to investigate the general biochemical role for each of the following components in Wesley's daily regimen:
 - Amlodipine
 - Benadryl
 - Clonidine
 - Ergocalciferol
 - Ferrous sulfate
 - Fludrocortisone
 - Lansoprazole
 - Levocarnitine
 - Prednisolone
 - Sulfamethoxazole-trimethoprim
 - Tacrolimus
 - Ursodiol

Section E – Development

Despite his metabolic fragility, Wesley has continued to grow and develop into a lively preschool-aged boy. He continues to need a feeding tube, since an inexplicable side effect of his disease is the inability to tolerate the feel of food in his mouth. He has constant diarrhea. He does not speak but he does squeal with delight and cry from frustration. He is learning sign language and he responds to Kar's requests and directions. He cannot (yet!) hold a pencil but he runs, jumps, and will sit still for a favorite video. He loves music, is fascinated with shadows, and enjoys playing in water. In short, he is in many ways a typical preschooler who happens to be living with propionic acidemia.

Part III – Caregiver Needs

Throughout all of Wesley's health crises, Kat has managed his round-the-clock feedings and other needs. She maintains an extensive spreadsheet with his various appointments and medications. However, she also needs to prioritize her own self-care and seek assistance and relevant resources so that she does not experience "burnout."

Question

1. If you found yourself unexpectedly in a situation like Kat's, what types of issues would you face? What types of support systems and resources would you need?

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