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UREA CYCLE REVIEW USING A CASE STUDY ON

ORNITHINE TRANSCARBAMYLASE DEFICIENCY

By

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A capstone project submitted for Graduation with University Honors

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Abstract

The subject of biochemistry has been historically challenging to master, as the discipline boasts a need for the application of the material since it broadly integrates biology, chemistry, and physics. Because the study of biochemistry can be extensive, introductory courses tend to be rigorous and content-heavy to cover foundational topics in a reasonable amount of time. Consequently, undergraduate students tend to favor surface-level memorization over critical analysis, which often results in lower retention of the material. The growing practice of case-based learning (CBL) activities in STEM undergraduate classes provides an active learning approach to improving student learning outcomes. To combat surface-level approaches and raise student retention of biochemical concepts, a CBL activity was created to be implemented in the Honors discussion sections of introductory biochemistry courses at the University of California, Riverside (UCR). This case will be submitted to the National Center for Case Study Teaching in Science (NCCSTS) at the University at Buffalo, a repository of scientific case studies accessible to educational institutions. At UCR, the 10-week course introduces nitrogen metabolism and the urea cycle around Week 8. That late in the quarter, students may find it overwhelming to learn the intricacies of the urea cycle and deem the topic less important to review than prior material. Through the creation of a CBL activity, the purpose of this project is to give instructors an active learning approach that reinforces student retention of biochemical concepts. In this case, the activity focuses on the urea cycle and the medical consequences when one of the enzymes, ornithine transcarbamylase, is dysfunctional.

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Table of Contents

Abstract 2
Acknowledgments 3
Introduction 5
Literature Review 6
    Why is Case-Based Learning Important? 6
    What is the Urea Cycle? 10
    About Ornithine Transcarbamylase Deficiency 11
Background to the Case Study 15
Learning Objectives 16
Classroom Management 16
The Case Activity: Atkins or Ammonia 18
Conclusion 23
References 24

Table of Figures

Figure 1: Urea Cycle Diagram 10
Figure 2: Urea Cycle and Pyrimidine Biosynthetic Pathway Relationship Diagram 14

Introduction

Biochemistry is a subject that has immense importance in the understanding of future clinical sciences. Biochemistry gives insight into the chemical relationship that guides the way of life and is thus a foundation for many careers in the biomedical sciences. Many students who are interested in pursuing some type of health profession are typically required to take an introductory biochemistry course. However, despite being called "introductory," biochemistry courses are rigorous, and challenge students to learn a variety of different topics in a condensed fashion. Between learning the properties of amino acids to drawing the metabolic pathways, it becomes difficult for students to fully understand and retain all the pieces of content. The difficulty in understanding the content results in a tendency to rely on surface-level memorization that can disappear once the big examination comes and goes. However, case-based learning (CBL) activities provide an opportunity to promote a deeper understanding of course content through connecting concepts to realistic scenarios (Kulak & Newton, 2015). Because many undergraduate students who take introductory biochemistry are pre-health-focused, an activity that revolves around a clinical scenario can encourage students to engage in the learning process.

At the University of California, Riverside (UCR), the 10-week introductory biochemistry course introduces nitrogen metabolism and the urea cycle around Week 8. By this point in the quarter, students may begin to feel overwhelmed by both new content and retaining previous concepts that they are expected to understand by the end of the course. Consequently, students may find difficulty in learning the intricacies of the urea cycle, because it may not be deemed as important as prior material and/or because it is presented quite late into the quarter. A possible reason why students may not deem the urea cycle as important as other metabolic pathways is

that the urea cycle contains fewer processes compared to a pathway like the Krebs cycle. Consequently, the students may feel more inclined to prioritize pathways that have a higher number of steps. In creating the case study activity, the main goal was to not simply have the students memorize the end products of the urea cycle but to have them evaluate the worth in understanding how the system is affected when an enzyme is dysfunctional. The case study also encourages students to actively recall and review both the urea cycle and previous concepts, such as amino acid characteristics, through the integration of the various concepts together in one case-based learning activity.

Literature Review

Why is Case-Based Learning Important?

Introductory undergraduate biochemistry courses are traditionally taught in a lecture format. There is a body of evidence to suggest that lecture-dominated curricula promote the passive learning process and therefore deters students from conceptual learning (Anderson et al., 2005). Passive learning is a model of instruction in which students receive information from the instructor and must internalize the information by themselves. However, that is not to say that instructors should completely abandon lecture-based curricula, especially in large class sizes and given its benefits in aspects of organization and presentation (Nasmith & Steinert, 2001). Lecturing has been the most predominant tool for information transmission in higher education, because it allows instructors to convey large amounts of information in a brief amount of time. As such, implementing the growing practice of providing supplementary, active learning activities to aid in the learning process becomes significant.

Active learning is a broad term used to describe several models of instruction that encourages students to engage and reflect on what they are learning in the classroom by having them take a participatory role in the learning process. Studies have linked active learning with an increase in student engagement and retention (Smith & Cardaciotto, 2011). Some of these models include facilitating small-group discussions within the larger class, student self-assessments, concept mapping, and case study exercises. The suggested benefits of active learning are that students are more involved, have more motivation, can receive immediate feedback, and can develop analyzing and evaluation skills, compared to passive learning. Because active learning methods typically require more class time, it is often used as a supplement when students have already acquired a foundational level of understanding in a particular subject matter. In a study comparing the impact of an active learning approach versus a traditional passive learning approach, the authors found that although there was no significant difference in broad subject matter learning outcomes, there was a significant improvement in class-specific learning outcomes for students exposed to the active learning approach (Michel et al., 2009). In terms of narrowly-defined learning goals, the study implied that students in the actively taught class had done a better job learning their class material than those who had only participated in a passive learning classroom.

There is a growing shift in education for student-centered learning through active learning because it focuses on giving students a deep learning experience by challenging them to understand and seek meaning from their material. By having students engage in an activity that forces them to reflect and access their understanding of the material, they can critically think and infer meaningful explanations to the problems. Meaningful learning effectively promotes the acquisition of knowledge that can integrate with other previously known concepts. Therefore, the

modality for engagement leads students to critically evaluate and retain the information (Michael, 2001; Yew et al., 2016). As such, there is a general need at institutions to incorporate more active learning strategies in the classroom.

Studies have found that a majority of students taking biochemistry courses use a low-engagement, surface-level approach to learning (Anderson et al., 2005; Minasian-Batmanian et al., 2006). For students, biochemistry may seem like a subject disconnected from the real world, as it requires the extensive memorization of complex pathways filled with chemical jargon. To address their struggles in learning the material, students typically take a surface-level approach by memorizing and regurgitating fragmented information as opposed to developing a deep understanding of connecting concepts. While short-term memorization of facts can help a student during the course, understanding specific concepts and being able to problem-solve are fundamental skills for success in their future careers. Because of their surface-level approaches, students struggle to show sustained conceptual knowledge of the presented material. Hence, there is a need to put more active learning methods into practice in biochemistry classrooms to help reinforce student learning and retention.

Case-based learning (CBL) is an active learning tool, used to enhance learning through taking contextualized real-life case scenarios and relating them to the students' prior knowledge. Case studies are often used to teach, supplement, or reinforce lecture material to enhance student participation in the class. Studies have found that CBL created effective learning environments, an increase in knowledge equal to or greater than passive learning, and correlations to problem-solving skills (N. Harris & Welch Bacon, 2019; Kulak & Newton, 2015; Nair et al., 2013). CBL can also empower students to learn due to the practical application of the knowledge to the world

outside of academia (Anderson et al., 2005; C. L. Harris et al., 1997). The self-empowerment can lead to a positive student attitude towards learning the class material and the discipline itself.

The case scenarios are generally written as problems that provide the student with the background of a clinical situation, along with supplemental information such as clinical signs, symptoms, and laboratory results. The students can then use their problem-solving skills to recall and apply their understanding of learned topics to realistic situations. Most CBL activities focus on using small groups of students to work together to solve the problems. By allowing student collaboration, the students can discuss and address any knowledge deficiencies. This allows students to develop a collaborative, team-based approach to their education.

The role of a lecturer or facilitator becomes a coach that leads and motivates students to find the answers to their questions within their notes (Hyun et al., 2017). If a case is well-written, studies have found that the scope of knowledge of the facilitator has no hindrance on the outcomes of the activities since it is centered around the prior knowledge of the students (C. L. Harris et al., 1997). Thus, supplemental instruction or discussion sections can greatly benefit from the utilization of case study activities. If implemented successfully, the use of these case studies can further the learning outcomes of classes/courses of undergraduate science students' comprehension.

The presented case study activity aims to remind students that the content they are learning is interconnected and relevant in the real world. The case study activity could further motivate students to pay more attention to the multi-faceted lessons found in biochemistry.

What is the Urea Cycle?

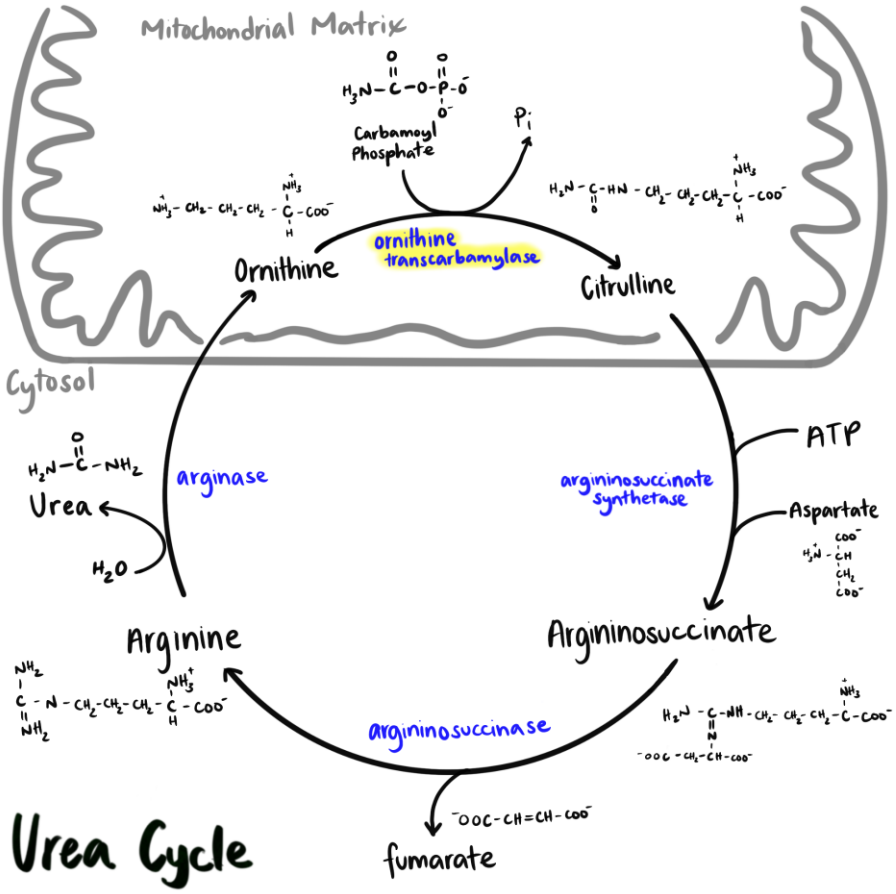

Figure 1: Urea Cycle Diagram

The urea cycle is a liver process that is the primary nitrogen disposal pathway. It converts ammonia into urea by the coordination of various enzymes. These enzymes include ornithine transcarbamylase, argininosuccinate synthetase, argininosuccinase, and arginase, as shown in Fig. 1. Ammonia, a byproduct of amino acid and nitrogenous base breakdown, is highly toxic to the human body because it is a central nervous system toxin. Ammonia toxicity, or hyperammonemia, occurs when the ammonia content in the blood supersedes the liver's capacity to eliminate it. In the brain, excess ammonia may induce changes in the transport of the excitatory amino acid neurotransmitter glutamate, alter brain energy metabolism, and change the

neuronal electric activity by inhibiting the generation of synaptic potentials (Ott et al., 2005). Therefore, it is necessary for the liver to convert toxic free ammonia into inert urea prior to undergoing excretion by the kidney.

About Ornithine Transcarbamylase Deficiency

Ornithine transcarbamylase is a mitochondrial urea cycle enzyme that catalyzes the formation of citrulline, a urea precursor, from ornithine and carbamoyl phosphate in the liver and small intestine. When ornithine transcarbamylase is dysfunctional, it is clinically presented as ornithine transcarbamylase (OTC) deficiency. Ornithine transcarbamylase deficiency is an inherited X-linked urea cycle defect, and is the most common genetic disorder of the urea cycle, with an estimated prevalence ranging from 1 in 14,000 to 1 in 77,000 people (National Institutes of Health, 2020). The gene for OTC deficiency, *OTC*, is on the X-chromosome. Therefore, hemizygous males will be predominantly affected, while heterozygous females may or may not develop the symptoms related to the disorder. OTC deficiency causes ammonia to accumulate in the blood because the pathogenic mutations in the ornithine transcarbamylase gene can cause the enzyme to be the wrong shape, the wrong size, or prevented from production. If the ornithine transcarbamylase enzyme is misshapen or missing, the enzyme cannot perform its function to stimulate the formation of urea. Consequently, ammonia builds up within the body, leading to hyperammonemia.

The pathogenic variations in mutations of the *OTC* gene result in variable severity of clinical presentations. The disorder can present itself as early-onset severe hyperammonemia in newborns to late-onset cases in adults. In late-onset cases in adults, the disorder is typically triggered by environmental stressors that cause hyperammonemic episodes, such as ingesting

excessive amounts of protein, invasive medical procedures, chemotherapy viral gastroenteritis, and metabolic stress that increases protein catabolism and ammonia production. Neonatal presentations are usually correlated with the absence of liver OTC activity, while late-onset presentations are correlated with partial OTC activity. Pathogenic variants in *OTC* genes include nonsense mutations, insertions, deletions, missense mutations, variants in the splicing of *OTC* mRNA, deletions and duplications within the OTC locus, and a variant in the *OTC* promoter. The effect of nonsense, insertion, and deletion variants result in the complete dysfunction of the *OTC* gene product because they disrupt the reading frame of the coding sequence (Lichter-Konecki et al., 1993). In contrast, missense variants on *OTC*, caused by the substitution of amino acids in either the active site or the hydrophobic core, change the stability of enzyme folding and activity and thus results in a partially functional enzyme. With regards to the effect of splicing, mutations near-consensus intron splice sequences and the last base pair of exons 1-9 almost always result in the absence of functional mRNA, while mutations causing novel splicing sites deep within *OTC* introns result in reduced levels of functional mRNA (Lichter-Konecki et al., 1993). When a family has a positive family history with OTC deficiency, DNA mutation analysis of the affected gene is the most reliable method for detecting the carrier state of females and for making a prenatal diagnosis.

The clinical signs and symptoms of OTC deficiency are a result of the large excess of ammonia affecting and deteriorating the central nervous system, particularly the brain. In hyperammonemia, blood ammonia is transported to the brain through the blood-brain barrier via diffusion and competes with potassium transporters. This causes both the pH and the membrane potentials of the brain to change. Under hyperammonemic conditions, the pH increases and the membrane potential decreases in the brain (Szerb & Butterworth, 1992). In addition, the excess

ammonia signals alpha-ketoglutarate in the brain to be turned into glutamate. The depletion of alpha-ketoglutarate affects the ability of the brain cells to make ATP via the Krebs cycle, causing the cells to have no energy (Ott et al., 2005). As a result, patients typically have neurological symptoms including confusion, lethargy, behavioral disturbances that can later progress to seizure, cerebral edema, and death.

Because ammonia is toxic and must be removed quickly, ammonia is stored and transported in the body via incorporation into its non-toxic forms of glutamine, glutamate, and alanine. However, because of the inability to excrete excess ammonia in OTC deficiency, the patients will show increased levels of ornithine, glutamine, glutamate, and alanine as well as decreased levels of citrulline and arginine. These abnormalities result from the inability to convert ornithine and carbamoyl phosphate into citrulline, causing the production and excretion of urea to be dysfunctional. In addition, due to the inability to properly enter the urea cycle, carbamoyl phosphate cannot be properly excreted and thus the excess carbamoyl phosphate is shunted into an alternative metabolic pathway called the UMP synthetic pathway for pyrimidine biosynthesis, as illustrated in Fig. 2. Orotic acid is an intermediate compound in the pyrimidine biosynthesis pathway (Brosnan & Brosnan, 2007). Consequently, patients with OTC deficiency also characteristically have an elevated concentration of urinary orotic acid.

Although OTC deficiency cannot be completely cured because it is a genetic defect, there are treatments to alleviate symptoms. These treatments include a low-protein diet, supplementation of arginine or citrulline, sodium benzoate, and in extreme cases, liver transplant and hemodialysis (Lichter-Konecki et al., 1993). Supplementation of arginine and citrulline is primarily meant to maximize ammonia excretion through the urea cycle by bypassing the ornithine transcarbamylase step. Sodium benzoate is used to divert ammonia from the defective

urea pathway to an alternative hippurate synthesis by way of the glycine cleavage complex (Häberle et al., 2012). Hemodialysis is a treatment that filters wastes, salts, and fluids in the blood through an artificial kidney called a dialyzer, which can remove ammonia from the blood by using a high flow rate (Anwar et al., 2014). The treatments overall are designed to lower ammonia levels by reducing amino acid catabolism, excreting the ammonia by bypassing the OTC enzyme, or by filtering out the ammonia externally to prevent any further detriment to the central nervous system.

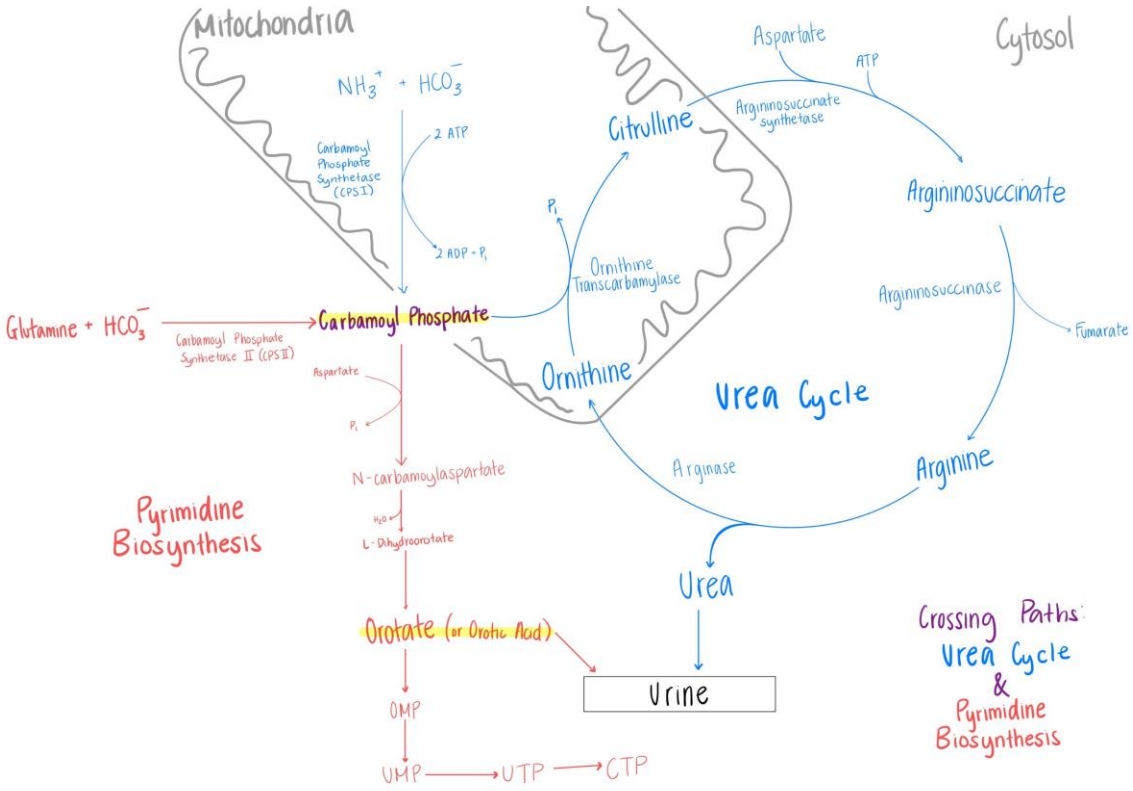

Figure 2: Urea Cycle and Pyrimidine Biosynthetic Pathway Relationship Diagram

Background to the Case Study

The case study presented is an exercise that reviews the biochemical urea cycle and what would happen if one of its enzymes, ornithine transcarbamylase, becomes dysfunctional. The story is based on actual medical reports but is fictitious in detail (Alameri et al., 2015; Ben-Ari et al., 2010; Choi et al., 2012; Panlaqui et al., 2008; Thurlow et al., 2010).

It begins with the fictitious case report of a man admitted to the emergency room after a loss of consciousness following a return from the local gym. The students play the role of a student shadowing a physician, investigating the case. During the examination, the patient displays several neurological concerns, and the local ER physician calls upon the student to work through and predict what is causing the symptoms, given abnormalities in the laboratory findings. Throughout the investigation, the student should discover that the patient's excessive amount of dietary protein from the Atkins diet has triggered the X-linked urea cycle defect, ornithine transcarbamylase deficiency. As a result of the inability to eliminate the ammonia byproduct from excessive protein catabolism, the patient began to suffer the effects of hyperammonemia on the central nervous system. The story ends with the student suggesting possible treatments that would help resolve the patient's symptoms and allow the patient to be discharged from the hospital.

This case was designed to reinforce the concepts of the nitrogen metabolic pathway, particularly the urea cycle, in an introductory biochemistry class. Students who do this case should have been introduced to the urea cycle and its respective enzymes, the Krebs cycle, and the chemical properties of different amino acids and their effects on the functionality of enzymes.

Learning Objectives

Upon completion of this case study, the students will be able to:

- Explain and identify the importance of the urea cycle.
- Predict the products and substrates present when a single enzyme of the urea cycle is dysfunctional.
- Understand how nitrogen is transported within the body.
- Make connections between different metabolic pathways.
- Be able to identify and explain the effect of amino acid substitutions on enzymatic activity.

Classroom Management

The case study activity is presented as an interrupted case to the students and is meant to be completed within a one-hour class period as group work. An interrupted case is characterized by a progressive disclosure of information, separated by stages. The instructor reviews each group's answers to a completed section before allowing the students to proceed to the next part. This case study is separated into three parts. The case should be presented after students have already been introduced to the foundational topics of nitrogen metabolism and the urea cycle. The students are encouraged to complete the activity without consulting their notes.

Part I introduces the case report involving the admission of a 21-year-old male patient to the hospital due to a sudden loss of consciousness upon returning from the gym. In this part, patient history, vital statistics, and blood panel work is provided. This part prepares the students to pay careful attention to observed abnormalities and consider the topic that they will be analyzing. After the initial introduction, this part is discussed as a class (20-25 students).

Part II and III are more directly involved with the concepts of nitrogen metabolism and the urea cycle. In these parts, the class is divided evenly into groups of 4 to 5 students, allowing

each student to work on the activity collaboratively. Part II primarily functions as a review from lecture material and incorporates more specific vital blood panel results that the students can analyze. Part III dives further and challenges students to analyze critically and stimulates recall of previously-learned concepts such as amino acid characteristics and the Krebs cycle. Questions presented in these sections highlight the idea that regardless of how seemingly distinctive metabolic pathways are, they are interconnected together. For example, one of the questions hints at the similarities of the isozymes carbamoyl phosphate synthetase I (CPS I) and carbamoyl phosphate synthetase II (CPS II), which are found in two separate pathways: the urea cycle and the pyrimidine biosynthetic pathway. The case study activity concludes with a detailed discussion of OTC deficiency with the class.

The case activity, presented on the next few pages, was written as a worksheet for students to complete in-class. The intent is for instructors to be able to separate and distribute each of the parts by pages. However, instructors may alter this type of presentation in any way that suits their classroom better, such as presenting the material on a slideshow. For example, instructors may opt to have the groups write their answers on a whiteboard and discuss the reasoning with the rest of the class or adapt the material as clicker questions.

In consideration of the recent COVID-19 pandemic, the distribution and handling of the case study can be modified to better fit remote settings. Modifications can be made regarding distribution, such as providing the students Part I as a pre-class assignment to be completed and submitted via a learning management system (e.g. Canvas). Group work can be facilitated by breaking up the students into groups via breakout rooms on online meeting room systems (e.g. Zoom) and having the students work on the parts via collaborative online workspaces (e.g. Google Slides).

The Case Activity: Atkins or Ammonia

Part I:

Case: Atkins or Ammonia

A previously healthy 21-year-old male was admitted to the emergency room of the local hospital after his mother witnessed his sudden loss of consciousness after returning from the local fitness gym. Prior to admission, he had intermittent lethargy, nausea, and vomiting over a one-week period. He had assumed that his lethargy was due to overexertion during one of his starting workouts. On arrival to triage, his vital signs were as follows: blood pressure 125/70 mm Hg, pulse rate 80 beats/min, and respiratory rate 16 breaths/min. The patient did not have fever, chills, or sweats. During the examination, he appeared disoriented and began to have slurred speech. He also complained of "feeling off" and "things creeping on his skin." Over the first 24 hours of admission, the patient began to become increasingly disoriented and aggressive. On the 36th hour, the patient began having seizures. You are shadowing your local ER physician, who would like your insight and help in determining what might be causing these symptoms.

THE INVESTIGATION:

Investigate medical history including current medications.

Results: We found the medical history was unremarkable for any chronic conditions. He had never had an episode of altered mental status or signs of liver disease.

Interview the patient's family to determine dietary habits.

Results: His mother informed us that in an attempt to become more fit, the patient had begun to adopt the fad Atkins diet, which consists of intaking low amounts of carbohydrates and an unlimited amount of protein and fat. He was taking a high-protein supplement in conjunction with joining the local fitness gym.

Test the blood for common poisons.

Results: No common poisons were found in a toxicology test.

Conduct a physical exam.

Results: After a physical examination of the abdomen, the liver did not appear larger than normal. The patient did not report any feelings of pain or tenderness in his abdomen.

BLOOD PANEL RESULTS:

DETERMINE BLOOD SERUM CONCENTRATIONS OF:

White Blood Cell Count (10^9/L):
Results: 12.7 (normal range: 4.5-11.0)
Hemoglobin (g/dL):
Results: 16.0 (normal range:13.8-17.2)
Platelets (10^9/L):
Results: 239 (normal range: 150-400)
Glucose (mg/dL):
Results: 96 (normal range: 60-100)
Blood Urea Nitrogen (mg/dL):
Results: 7 (normal range: 6-20)
Lactate (mg/dL):
Results: 16.0 (normal range: 4.5-19.8)
Aspartate Aminotransferase (U/L):
Results: 80 (normal range: 8-33)
Alanine Aminotransferase (U/L):
Results: 58 (normal range: 4-36)
Bilirubin (mg/dL):
Results: 1.02 (normal range: 0.1-1.2)
Ammonia (µg/dL):
Results: 541 (normal range: 15.0-45.0)

1. Based on your current information, what possible kind of disorder(s) may be afflicting the patient?
    a. Glycogen storage disease
    b. Diabetes mellitus
    c. Urea cycle disorder
    d. Epilepsy
    e. Stroke
2. Give a reason for why you chose the above disorder(s).

Part II:

Result: Based on the current evidence, you conclude that the patient is inflicted by a urea cycle disorder due to the excessive amount of ammonia in the bloodstream and no signs of liver disease. Excess ammonia in the brain can cause neurological damage by inducing changes in the transport of the excitatory amino acid neurotransmitter glutamate, altering brain energy metabolism, and changing the neuronal electric activity by inhibiting the generation of synaptic potentials.
The doctor agrees and puts the patient under a session of hemodialysis to reduce the amount of ammonia in the blood to prevent further neurological damage. Hemodialysis is a treatment that filters wastes, salts, and fluids in the blood through a dialyzer, a device that acts as an artificial kidney.

DETERMINE SPECIFIC PLASMA AMINO ACID CONCENTRATIONS OF:

Arginine (µmol/L):
Results: 53 (normal range: 68-104)
Citrulline (µmol /L):
Results: 10 (normal range: 20-60)
Glutamine (µmol/L):
Results: 1300 (normal range: 420-700)
Glutamate (µmol /L):
Results: 140 (normal range: 10-50)
Ornithine (µmol /L):
Results: 26 (normal range: 20-70)

DETERMINE SPECIFIC URINE AMINO ACID CONCENTRATIONS OF:

Glutamine (mmol/mol creatinine):
Results: 170 (normal range: <100)
Orotic Acid (mmol/mol creatinine):
Results: 120 (normal range: <5)

3. What is the purpose of the urea cycle? In what organ does the urea cycle take place?

4. What key amino acid(s) can store ammonia?

5. The unusual levels of citrulline could be explained by the loss of function of which enzyme? Draw the reaction catalyzed by this enzyme.

6. Name the specific cellular compartment where the above reaction occurs.

7. Orotic acid is an intermediate in pyrimidine biosynthesis. Why would there be an increase in the amount of orotic acid excreted in relation to this urea cycle disorder? (Hint: Pyrimidine biosynthesis involves a reaction with aspartate and carbamoyl phosphate.)

8. Based on the information, what is the most likely diagnosis for this patient?
    a. Ornithine transcarbamylase deficiency (OTC deficiency)
    b. Carbamoyl phosphate synthetase 1 deficiency (CPS1 deficiency)
    c. Arginase deficiency
    d. Argininosuccinate lyase deficiency (ASL deficiency)
    e. Argininosuccinate synthetase deficiency (Citrullinemia)

9. Considering patient history, what could have possibly triggered the disorder to become unmasked in this patient?

Part III:

10. A DNA analysis of the affected gene showed a missense mutation that led to an isoleucine to methionine substitution in exon 5. Why would this amino acid change be significant in the function of the enzyme?

11. Brain damage can be caused by hyperammonemia because under high ammonia conditions, alpha-ketoglutarate in the brain is turned into glutamate. What metabolic pathway could be affected by this reaction? What is the effect of this other metabolic pathway being compromised?

12. What treatments could be suggested to reduce the effects of the determined deficiency? Select all that apply.
    a. Increase protein intake
    b. Supplementation of arginine to improve overall function of urea cycle by allowing for urea creation and ammonia elimination
    c. Lactulose (a type of laxative) therapy to reduce the amount of ammonia in the blood by drawing ammonia into the colon to be excreted
    d. Sodium benzoate to divert ammonia from the defective urea pathway to an alternative usable pathway (specifically hippurate synthesis by way of the glycine cleavage complex)

Conclusion: Within the next few days after undergoing proposed treatments, the patient's serum ammonia level normalized, and the patient's mental status returned to normal. The patient was discharged home after 2 weeks with instructions to continue taking the prescribed medication and to discontinue the Atkins diet. Because OTC deficiency is an inherited X-linked urea cycle defect, the patient and his family were advised to seek genetic counseling to evaluate risk for other relatives to be affected by the OTC gene variant.

Conclusion

The impetus for developing this case study was my desire for students to appreciate the importance and interconnected nature of biochemistry, in particular the urea cycle. By using a real-life scenario, students can evaluate how abnormalities in biochemical pathways can be a possible cause of medical symptoms. The use of case studies can open opportunities for students to engage in a more personal approach to understanding the dynamic nature of biochemistry and opposing the belief that the subject is a static set of principles.

Currently, this case study has only been employed in one general biochemistry honors course discussion at UCR. The students in the discussion section generally enjoyed the integration of the case study. Based on preliminary feedback from these students and evidence from current literature, this case study could be promising in helping long-term retention of the concepts related to the urea cycle. This activity could be used in future studies to collect and analyze large-scale data to see if the overall retention of the class material is enhanced and whether the broader impact is beneficial to student learning. There is a potential for these studies to explore the impact from student attitudes, demographics, presentation medium, as well as quantify the degree of success from case-based learning.

This case will be submitted to the National Center for Case Study Teaching in Science (NCCSTS) at the University at Buffalo, a repository of scientific case studies accessible to educational institutions, to open opportunities for more classes to employ this case study. Hopefully, other instructors can further employ and continue to use this case study to engage students in active learning.

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