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Introduction to Biochemical Genetics from the Clinical Laboratory Prospective: A Case-Based Discussion

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Abstract

Introduction: Inborn errors of metabolism (IEM) are individually rare, but their cumulative frequency is high. Most importantly, IEM are in the differential diagnosis for common clinical emergencies and childhood illnesses. Biochemical genetics (BCG) testing is used to diagnose IEM or follow-up with patients after treatment. A basic grasp of the strengths and limitations of biochemical testing is critical for clinicians to understand test results, identify when to seek a consultation with a specialist, or explain results to patients. **Methods:** This resource is designed as an introduction to BCG testing for aminoacidopathies and urea cycle disorders, and includes eight cases. The resource was first developed for the Genetic Counseling Graduate Program at the University of Utah School of Medicine, and used in the last 2 years in small-group settings, where students were each engaged with one case (eight per session). **Results:** Overall, students gave high ratings to the effectiveness of the examples used, and the interactive format encouraged students' questions. The resource has been tested with medical students and residents rotating through the Maternal Newborn Care Unit at the University Hospital. In this setting, a small-group case-based discussion was used. As expected, prior knowledge of IEM or BCG testing was low. Confidence in evaluating BCG testing after completing the learning activity improved. **Discussion:** This resource facilitates the integration of specialized knowledge of IEM in a primary care-oriented setting. Genetics counseling students' feedback demonstrated the overall success of this activity in the specialized, genetics-oriented setting.

Keywords

Genetics, Inborn Errors of Metabolism, Biochemical Genetics, Newborn Screening, Newborn Infant Screening, Amino Acids, Aminoacidopathies, Urea Cycle Disorders

Educational Objectives

By the end of this session, learners will be able to:

1. Define inborn errors of metabolism.
2. Review the key concepts in laboratory testing as applied to the diagnosis and follow-up of inborn errors of amino acids metabolism.
3. Employ these key concepts and prior knowledge to critically discuss the questions posed by the case studies.

Introduction

Inborn errors of metabolism (IEM) are a very broad group of disorders, clinically presenting either acutely as a medical emergency, or as a chronic, progressive condition.¹ Because of their variability in clinical manifestations, IEM are in the differential diagnosis of several common conditions such as sepsis, adrenal insufficiency, and congenital heart disease. Specific biochemical genetics (BCG) testing is routinely performed on patients, especially pediatric, to exclude IEM. Correctly identifying these conditions is paramount since prompt and specific treatment is, in most cases, life-saving. Newborn screening (NBS) programs aim to increase early presymptomatic detection and improve outcomes in most cases.²⁻⁴ Many NBS programs now include IEMs, increasing the number of newborns requiring confirmatory testing for a

Appendices

- A. PowerPoint Presentation .pptx
- B. Case Studies.docx
- C. Pathways Handout.docx
- D. Pre and Posttest.docx

All appendices are peer reviewed as integral parts of the Original Publication.

positive screen. The primary care physicians play an important role in supporting the newborn screening system by informing families of a positive newborn screen, arranging confirmatory testing, and seeking referral to subspecialties when an IEM is confirmed.^{5,6} However, physicians recognize a lack of training as a barrier to adequately provide follow-up care for these children.^{7,8} Moreover, physicians acknowledge the lack of knowledge about genetic tests and the need for more education.⁹ Evaluating the results of these tests can be daunting for health care providers unfamiliar with these conditions. Seeking a consultation with a metabolic specialist is ideal, but increasingly difficult due to the scarcity of board-certified medical geneticists.¹⁰

Understanding the significance of laboratory findings and the limitation of the information provided by testing is critical to patient care. Providing detailed examples of test results within the context of clinical cases can improve disease awareness and comfort level with evaluating test results. Three educational resources currently available on MedEdPORTAL provide a review of IEM¹¹ and examples of clinical presentation and laboratory testing suggestive of IEM.¹²⁻¹³ The limited amount of resources available, covering a limited number of specific conditions or laboratory testing examples, emphasizes the difficulty in accessing examples of BCG testing. Accessing detailed examples of BCG testing performed on patients with IEM can be difficult, especially outside specialized laboratories. Here, we provide educational material focused on examples of BCG testing while highlighting both the information conveyed to physicians and the limitations of testing. We aim to provide the necessary tools to integrate this information in the medical training of genetics and nongenetics specialists.

Clinical case studies have been extensively and successfully used to engage students.¹⁴ A recent study examining genetics curricula in US and Canadian medical schools found that approximately only half of the time is spent in formal lecture setting, and small-group and problem-based sessions account for about 30% of curriculum time.¹⁵ Availability of educational material focused on BCG testing using a clinical case format will improve clinicians' training and will allow a better understanding of these esoteric laboratory findings, ultimately improving patient care.

Methods

The objective of this educational material is to familiarize learners such as medical students, genetic counseling (GC) students, residents, laboratory fellows, and clinicians in nongenetics specialties to the intricacies of BCG testing results and interpretation. Although this resource would be best used with students that possess a basic knowledge of biochemistry and genetics, introductory slides in the included PowerPoint presentation contain the background key concepts, and a review of important biochemical pathways to guide students in critically discussing the cases. The cases provided were referred to Associated Regional University Pathologists (ARUP) Laboratories (Salt Lake City, UT,) for a possible or confirmed metabolic disorder and contain some limited clinical information (provided at the time of testing) as well as the results of the biochemical tests performed. The BCG testing results and limited clinical information were obtained after a retrospective chart review of existing data after obtaining IRB exemption.

This resource was first developed for the Genetic Counseling Graduate Program at the University of Utah School of Medicine to introduce GC students to BCG test results for the diagnosis or follow up of patients with aminoacidopathies and urea cycle disorders. The usefulness of this resource for nongenetics specialists was then tested by a primary care pediatrician with medical students, interns, and pediatrics and family medicine residents rotating through the Maternal Newborn Care Unit at the University Hospital. The instructor does not have to be an expert in biochemical genetics, since the specific points about biochemical pathways and laboratory testing are provided in the resource.

This resource has been designed to be used in a small group setting (four to eight students), to allow for each student the opportunity to discuss at least one case. This presentation, including all eight cases, will take approximately 90 minutes (with student participation); however, this activity needs less time if only some of the case studies are discussed. The first 30 minutes of the presentation allow for the instructor to define IEM and cover BCG testing key concepts, while the final 60 minutes are used to engage each

student with one of the eight cases. The activity can be broken down in two or three shorter sessions if necessary. After the background introduction, the instructor reads the clinical vignette for a case and then asks a student to describe the results of testing, which in some cases will include the diagnosis. A question slide is provided to help guide the students as they critically discuss the results interpretation. The answer to the question is presented in the following slides. Further points for discussion are included in the final slides. To help students correctly identify the metabolic blocks affecting the patients in these cases without having to memorize pathways, a handout illustrating these pathways is also provided.

The resource includes a PowerPoint presentation (Appendix A), with 16 slides summarizing the key concepts necessary for the case discussion and approximately five to seven slides per case; a case studies document (Appendix B) containing the background information and a brief description of each case (clinical vignette, results interpretation, additional points for discussion) for the instructor; a handout with simplified overviews of metabolic pathways (Appendix C); and a pre-/posttest document (Appendix D) to assess knowledge.

Results

This resource was first developed for the Genetic Counseling Laboratory Rotation, which aims to expose first-year students to results and interpretation of complex clinical genetics tests. The rotation takes 3 weeks, and includes several small-group activities and case discussions. Specifically, this resource was designed to focus on BCG testing for aminoacidopathies and urea cycle disorders and has been used successfully in the last 2 years by the instructor, a biochemical geneticist. The allotted time for this activity was 90 minutes. Minor changes were made from the first to the second year based on student feedback and instructor's self-reflection. Given the Genetic Counseling Graduate Program's focus on genetics and genomics testing (including BCG), and the prerequisites to this rotation (which include a semester-long class in biochemical genetics), the GC students possessed a moderately advanced understanding of this topic.

As a postsession evaluation of the resource, the students provided feedback on a survey featuring both a 5-point Likert scale (5 being high/strongly agree), and open-ended questions. When asked if the resource was appropriate and contained useful examples to illustrate the material, the students rated the effectiveness of the examples in a positive light (4.88 out of a maximum score of 5; $n = 16$). Some students specifically commented on the usefulness of the case discussion, for example: "Really enjoyed using case examples to illustrate specific laboratory findings and relevance to testing." Moreover, they agreed that the interactive lecture format encouraged student questions (4.75 out of 5) and provided an effective use of time (4.94 out of 5).

To further determine the usefulness of this resource, a general pediatrician used the same interactive lecture with medical students ($n = 4$) and residents in either pediatrics or family medicine ($n = 15$) rotating through the Maternal Newborn Care Unit at the University Hospital. Primary care pediatricians routinely provide care to newborns in critical conditions, in which IEM is suspected, or newborns with a positive family history for IEM. However, they are not specialists in biochemical genetics or laboratory medicine.

To accommodate the busy clinical environment, the resource was broken down into two or three sessions (30 or 45 minutes long, respectively) during the week-long rotation, and used for a total of 4 weeks (from October to December 2016) in a small group setting (four to six students). The instructor reviewed the background key concepts in the first session and then facilitated the case discussion in the following sessions.

To evaluate this resource, the medical students and residents were asked to complete a standard postsession evaluation, rating the learning activity using a 10-point Likert-type scale (10 being very high/strongly agree). Students mean ratings are as follows ($n = 19$):

- The clarity of the information provided; mean = 7.79.
- The overall quality of the learning activity; mean = 7.68.
- The overall quality of the teaching/instruction; mean = 8.00.

- The instructor's ability to stimulate you to think more deeply about the subject; mean = 8.16.

Because several students commented on the difficulty of remembering enzyme names and pathways (please see the following comments), a handout (Appendix C) was added containing the pathways discussed in the cases.

- "By far, the visuals (pathways) and the cases are most helpful. Perhaps, a handout of the common biochemical pathways could be helpful, especially if distributed in advance. That way, it is easier to practice going through."
- "Would be helpful to have print out of the important metabolic pathways; was often a bit of information overload at times without having a reference for learners to return to for clarity."

To gauge the knowledge level of the students before the activity, they were asked to rate prior knowledge of IEM and BCG testing. Although possibly higher than other nongenetics specialties since both pediatricians and family care physicians do provide care to newborns and children with a suspected or known IEM, and 60% of the students were residents in these specialties, their knowledge of IEM was rated low: mean = 4.26 (1 = no prior knowledge; 10 = extensive knowledge). Prior knowledge of BCG testing was, as expected in view of the esoteric nature of these tests, rated even lower: mean = 3.79. Students rated the confidence achieved in evaluating the results of amino acid testing after the completion of the learning activity as 6.16 on average (10 being very high).

Discussion

This resource was initially designed to offer case examples from the laboratory perspective to familiarize GC students to BCG testing for aminoacidopathies and urea cycle disorders within a week-long rotation at ARUP laboratories. The case studies were chosen to illustrate both the information provided by BCG testing, and some of the pitfalls to consider when interpreting that information. The main objective was to discuss complex testing results and interpretation with first-year students after several lecture-based courses had covered the background information on genetic disorders, specifically IEM. However, the student responses to this learning activity and the postcourse evaluation confirmed the effectiveness of student-centered activities, such as this interactive case-based discussion, as helping to achieve a better understanding and recollection of the information presented when compared to traditional lecture-based courses.¹⁶ In addition to a review of topics taught earlier, this activity allowed students to use the information in a context that mimics real-life clinical practice. A student commented: "I had not been able to apply what I had learned in Biochemical Genetics class until this rotation."

GC student feedback showed the overall success of this activity in a specialized, genetics-oriented setting. Because of the relative rarity of IEM and the difficulty in procuring examples of BCG test results outside of specialized laboratories, this resource benefits nongenetics specialists such as primary care physicians who are tasked with caring for infants with a positive newborn screen.^{5,6} The lack of training impacts the confidence level in interpreting results and the ability to adequately provide follow-up care for these children.^{7,8} Moreover, the emerging trend in medical education is to integrate genetics teaching within other disciplines by using clinical examples and interactive activities.¹⁴⁻¹⁶ This resource provides examples of esoteric laboratory testing results that can solidify knowledge in metabolic pathways and IEM, emphasize the importance of considering rare conditions in the differential diagnosis of common medical emergencies, and highlighting the use of laboratory medicine for the follow-up of patients treated for genetics conditions.

The usefulness of this resource within the primary care setting was tested by a pediatrician with medical students, interns, and pediatrics and family medicine residents. The confidence level in evaluating the results of amino acid testing improved after completing the learning activity. The mean score of 6.16 (10 = very high; $n = 19$) is fairly high, considering the low initial knowledge of IEM (4.26) and BCG testing (3.79) (1 = no prior knowledge; 10 = extensive knowledge). It would be interesting to assess this resource within nonmedical settings such as an undergraduate biochemistry course. Unfortunately this was outside the authors' educational practice. However, the modular nature of this resource, organized in cases, lends

itself to be used within very different contexts. For example, case #6 (patient with Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome) may be used to illustrate the effect of an impaired intracellular transporter when teaching cellular trafficking to undergraduate students.

Using this resource with larger groups is possible; however, the authors believe that it would significantly limit the opportunity for student engagement. To evaluate the sessions, a pre- and posttest are included to assess the improvement in BCG-specific knowledge (not utilized in our courses prior to publication).

In our opinion, the instructor's role is to primarily facilitate discussion and not to serve as an expert on IEM or BCG testing, and they may easily prepare for this activity by reviewing the PowerPoint presentation, the case studies provided, or other publically available material. However, in our study the resource was administered by a pediatrician, who, although not an expert in BCG testing, routinely provides care to newborns at risk of IEM. Interestingly, during two out of the four rotations in the Maternal Newborn Care Unit, when testing this resource, there were two newborns affected with a metabolic disorder. Both were eventually diagnosed with ornithine transcarbamylase deficiency, a urea cycle disorder. An infant boy presented acutely and an infant girl was tested because of a positive family history. In both cases, BCG testing was ordered together with a metabolic specialist consultation. Anecdotally, the occurrence of these cases during the rotation greatly increased the interest of the group of students in the activity. It is reasonable to speculate that in view of the IEM prevalence in infancy and childhood, medical students or residents rotating in pediatric specialties or sub-specialties would benefit from this activity, as they are learning about BCG testing when they are most likely to care for these patients.

Overall, we consider our experience a successful proof-of-concept that it is possible to integrate biochemical genetics and laboratory medicine, both considered specialized knowledge and somewhat removed by daily clinical practice, in a primary care-oriented setting.

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Ethical Approval

Reported as not applicable.

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