PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "Approach to Thalassemia." These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Approach to Thalassemia Part 1:

Developed by Ann Tran, and Dr. Catherine Corriveau-Bourque for PedsCases.com.
November 20, 2017

Objectives

1. Review the basic physiology of hemoglobin
2. Define hemoglobinopathy and review the alpha and beta globin chain hemoglobinopathies
3. Develop a basic understanding of the epidemiology, inheritance and clinical presentations for alpha and beta thalassemia
4. List key investigations that can help confirm the thalassemia diagnoses
5. Discuss the appropriate management for alpha and beta thalassemia patients

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Introduction

Thalassemia is a broad and complicated topic. The understanding of thalassemia is important as our population continues to diversify. Approximately 5.2% of the world's population carries a clinically significant hemoglobin variant (including but not exclusive to thalassemia). Generally, people with hemoglobinopathies have originated from malaria endemic countries; however, with migration, hemoglobinopathies now have a more global distribution. (1) Therefore, it is important as a clinician to recognize thalassemia patients and adequately counsel people who have thalassemia trait. Part 1 of this podcast will provide a brief overview of normal hemoglobin (Hb) physiology and discuss alpha thalassemia. Part 2 will focus on beta thalassemia and provide a summary of thalassemia management. For a general approach to pediatric anemia, please see the two-part podcast series for Anemia in children.

Case 1

Here is a case to start us off:
You are on an elective in a medical genetics clinic and are about to meet a couple looking to have their first child together. Tahir and Nafia are both 26 years-old and immigrated from Turkey in their childhoods. They both deny allergies and are on no medications, aside from a prenatal

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vitamin that Nafia just started. They are generally healthy adults with no significant past medical or surgical histories. However, Nafia mentioned to her family physician that she recently heard 'thalassemia' runs in her family. She believes someone mentioned she was slightly anemic in the past but told her to try and increase her dietary iron intake. Since the couple were planning to have a baby together, their family physician referred them to genetics to discuss thalassemia, whether genetic testing is indicated and the risk of their child having thalassemia.

Background

Before we dive into talking about problems with hemoglobin, let's talk about normal hemoglobin physiology. Hemoglobin is made up of a tetramer of globin chains, heme and ferrous iron and allows for the transport of oxygen to tissues. During late fetal development, most of hemoglobin is fetal hemoglobin (HbF) which is composed of two alpha globin chains and two gamma globin chains. HbF has a greater affinity for oxygen than adult hemoglobin (HbA) which is necessary for binding oxygen from maternal circulation. In-utero, red blood cells (RBCs) are produced in extra-medullary sites such as the liver and spleen. After birth, gamma globin production decreases as beta globin production increases to produce HbA. HbA is composed of two alpha and two beta globin chains and contributes to the majority of hemoglobin. Additionally, this production moves away from areas such as the liver and spleen and occurs predominantly in the bone marrow. Keep these areas of RBC production in mind as they will be important in the clinical manifestations of thalassemia. Another type of hemoglobin that contributes to our total hemoglobin includes HbA_2 which consists of two alpha and two delta globin chains. (2)

Hemoglobinopathy

Now let's explore some problems with hemoglobin. Hemoglobinopathies are inherited diseases that lead to quantitative and/or qualitative disorders of globin chain synthesis. Thalassemia is an example of a quantitative hemoglobinopathy and leads to insufficient globin chain production. (2) The most common thalassemias occur because of inherited alpha and/or beta globin gene mutations which results in an imbalance in the production of alpha and beta globin chains. Anemia occurs when abnormal Hb synthesis leads to premature destruction of erythroid precursors in the bone marrow and/or when Hb precipitates in mature erythrocytes leading to red cell membrane damage and subsequent hemolysis. (3)

In terms of nomenclature, the milder thalassemias with fewer deletions/mutations are referred to as 'silent carriers' and 'thalassemia trait.' The potentially more severe thalassemias with more gene mutations are referred to as 'disease.' Thalassemia disease includes non-transfusion dependent (NTDT) and transfusion dependent thalassemia (TDT). TDTs require red blood cell transfusions to sustain life whereas NTDTs at most require intermittent transfusions for symptomatic management but have a wide spectrum of disease including patients who are fairly asymptomatic. We will further explore these during our discussion about disease management in parts 1 and 2.

Who is affected by thalassemia and how do they inherit it?

Many hemoglobinopathies are believed to have evolved as protective mechanisms against malaria. Therefore, the countries that tend to have the highest number of affected people originate from the malaria belt. Alpha and beta thalassemias are commonly seen in African, Mediterranean, Middle Eastern, South Asian/Indian and South East Asian populations. Therefore, patients' ethnicities are an important component of investigating thalassemia and should always be respectfully asked about. (3)

In part 1 of this podcast, let's look at the genetics of alpha thalassemia. We will address the genetics of beta thalassemia in part 2.

There are two alpha genes on each chromosome 16. That means that we inherit two copies of alpha genes from each parent resulting in a genotype that has 4 alpha genes in total. Most commonly, alpha thalassemia presents when there have been deletions of these genes. Keep in mind that there are various mutations in addition to gene deletions that also lead to genotypic variants causing thalassemia. (2) In general, the more gene deletions and/or mutations a patient has, the more severe the anemia and overall symptoms.

With the background knowledge covered, let's start exploring alpha thalassemia in some more detail.

Genotype	**Phenotype**
αα/α-	Patients with one alpha gene deletion are silent carriers; their alpha globin deficiency is mild and therefore the production of HbA is not significantly affected. Patients are not anemic and are asymptomatic.
α-/α- or αα/--	Patients with two alpha gene deletions have alpha thalassemia trait; their alpha globin deficiency is more than in the silent carrier type and their HbA production is mildly reduced. The patients are typically asymptomatic and present with microcytosis. Their haemoglobin may be normal to slightly reduced.
α-/--	Patients with three alpha gene deletions have HbH disease; they have a more significant alpha globin deficiency leading to the formation of beta globin tetramers (also known as HbH). In the deletional form of HbH disease, the remaining alpha globin can generally compensate such that most patients have a microcytic anemia (baseline Hb approximately 90 g/L) and chronic hemolysis. Less frequent variants of this condition (non-deletional HbH) have a more severe phenotype.
--/--	Patients with deletions of all four alpha genes have no alpha globin production leading to Hb consisting of only gamma globin chains (also known as Hb Barts). The patients typically die in-utero or shortly post-natally without intrauterine transfusion support.

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History and Physical Exam

Patients who are silent carriers or who have alpha thalassemia trait are typically asymptomatic and have unremarkable physical exams. These patients tend to be diagnosed based on family history or have an incidental finding of a low mean corpuscular volume (MCV)/microcytosis and possible mild anemia. In HbH disease, the age of diagnosis can vary from within the first years of life to adulthood. There is a wide spectrum of disease from asymptomatic to requiring intermittent transfusions. Symptoms can include fatigue, poor feeding or appetite and dyspnea or poor exercise tolerance. On exam, patients can appear jaundiced and may have distended abdomens with hepatosplenomegaly or have an unremarkable exam. For Hb Barts, patients are typically detected in-utero by ultrasound and/or genetic testing. Since HbF cannot be produced, fetuses develop severe anemia resulting in features of hydrops (edema, ascites, pleural effusions, hepatomegaly) between 22-28 weeks gestations (4). Intrauterine transfusions are necessary to carry such infants to term.

Investigations

Abnormalities on a CBC are often the only reason a patient may be worked up for thalassemia. A CBC and peripheral blood smear are key initial investigations. The CBC will generally show thalassemic indices: microcytosis and increased red blood cells with or without a component of anemia. On the blood film, there can be hypochromic, microcytic RBCs with mild poikilocytosis including target cells. Essentially that means there are paler, smaller red blood cells that have varying morphologies/shapes.

A Mentzer index is the calculated ratio of MCV to RBCs and can be used when microcytosis is present to help guide further investigations. A ratio >13 is suggestive of iron deficiency anemia (IDA) and a ratio <13 is suggestive of thalassemia. (5) If indicated, iron studies should be ordered as thalassemia can initially be difficult to distinguish from IDA. These patients are often inappropriately managed with iron supplementation based on the assumption that a microcytic anemia is due to iron deficiency.

Next, a hemoglobinopathy investigation should be ordered to help distinguish alpha and beta thalassemia. There are a variety of tests available for this such as high-performance liquid chromatography (HPLC), electrophoresis etc. These tests are done with the goal of semi-quantitatively assessing the Hb types that are contributing to a patient's total hemoglobin. Alpha thalassemia patients typically have normal hemoglobinopathy investigations; therefore, if alpha thalassemia is suspected based on thalassemic indices, these patients will likely get genetic testing.

Management

Alpha thalassemia silent carriers and traits are clinically asymptomatic and do not require any management.

HbH disease is a type of NTDT. The majority of patients have deletional mutations, resulting in mild anemia and mild splenomegaly with no significant impact on activity level or quality of life

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outside of periods of stress like infections. A smaller subgroup of patients with non-deletional mutations have a more severe phenotype with more hemolysis and a lower baseline Hb.

Going back to the first case, with this background knowledge you now feel more prepared talking to Tahir and Nafia about this blood disorder. You ask for more history and Nafia denies any symptoms of anemia. She feels her diet is relatively balanced and has no bleeding symptoms, aside from monthly periods. Going into family history, she believes it was a cousin of hers who was told he had thalassemia. His diagnosis was incidental as he and the rest of the family have been healthy. You ask if Tahir and Nafia could possibly be related and they tell you no. On exam, Nafia appears well and there are no significant physical findings. Her family physician did some recent investigations which showed a Hb of 108 g/L, MCV 70 fL and a peripheral blood smear showing hypochromic, microcytic anemia with some target cells. Using your EMR, you look back on previous CBCs that Tahir has which show an approximate baseline Hb of 140 g/L and an MCV of 78 fL.

What do you think is going on here? How will you counsel the family?

You discuss the benefits and risks of genetic testing and the couple is agreeable to go ahead with investigations. A couple months later, molecular testing for Nafia demonstrates 2 alpha gene deletions on a single chromosome which confirms your working diagnosis of alpha thalassemia trait. Since Nafia and Tahir were initially coming in to discuss thalassemia and risks to the baby, Tahir also had molecular testing done which showed 1 alpha gene deletion. Alongside the genetic counsellor, you discuss that there are equal chances (all 25%) that the baby could have a normal genotype, be a silent carrier, have alpha thalassemia trait or have HbH disease. Using what you learned previously about the phenotypes, you counsel them about the spectrum of HbH disease and that all other possibilities would be clinically asymptomatic.

In summary, we have discussed that hemoglobinopathies are inherited disorders that affect globin chain synthesis. These disorders are prevalent in African, Mediterranean, Middle Eastern, South Asian/Indian and South East Asian populations. Thalassemia is a common condition clinicians will see as our population continues to diversify. Alpha thalassemia is commonly due to gene deletions and there are varied presentations depending on the inherited genotype. Normally, we have four alpha genes in total and if one or two genes are affected, patients are asymptomatic. When three genes are affected, the presentations can vary from asymptomatic microcytic anemia to symptomatic anemia requiring transfusions. When all four genes are affected, fetuses require intrauterine transfusions to sustain life. Clinical findings of alpha thalassemia are non-specific and may include poor feeding, fatigue, dyspnea, jaundice and hepatosplenomegaly. Laboratory findings include a low MCV, low Hb and anisopoikilocytosis on a peripheral blood film. Additional investigations include hemoglobinopathy screens and genetic testing.

Now that we have discussed alpha thalassemia, let's go to part 2 of this podcast to have a closer look into non-transfusion and transfusion dependent beta thalassemias.

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Approach to Thalassemia: Part 2

Hi everyone, welcome to the second part of the approach to thalassemia podcasts. In this second half, we will review beta thalassemia and delve further into the management of beta thalassemia patients. The objectives for this two-part podcast on thalassemia include:

Objectives

1. Review the basic physiology of hemoglobin
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4. List key investigations that can help confirm the thalassemia diagnoses
5. Discuss the appropriate management for alpha and beta thalassemia patients

In part 1, we discussed that hemoglobinopathies are inherited disorders of globin chain production. These disorders are typically seen in people from the malaria belt locations including people of African, Mediterranean, Middle Eastern, South East Asian and South Asian/Indian descents. Alpha thalassemia occurs predominantly due to gene deletions and has variable presentations. Commonly, patients are investigated when a low mean corpuscular volume (MCV) is incidentally seen on a CBC. For a full background into hemoglobinopathies and details of alpha thalassemia, please listen to Part 1.

Case 2

You are a third-year medical student rotating through the pediatric emergency where you meet Kal, a 6-month-old male brought in by his parents because he has recently been irritable with poor feeding. On history, you elicit that the pregnancy was unremarkable, Kal was born at 39 weeks via C-section with no post-natal complications. His parents deny any URTI symptoms or cough and no N/V or diarrhea. They note that he has been less playful than usual but his sleeping habits are unchanged and he is easily rousable. His parents also describe that he has been gaining weight but seems smaller than his two siblings when they were this age. They were not particularly concerned about the weight because they were told his growth curves have been relatively normal. He drinks breastmilk and just started trying cereals. Kal has no allergies that they know of, is taking Vitamin D and has not had significant medical conditions thus far. They have not traveled anywhere since his birth and his immunizations are up to date. His parents and siblings, who are 4 and 2 years of age, have no significant past medical or surgical histories to date.

On exam, his blood pressure is 75/45, heart rate 150, respiratory rate 30, SpO_2 95% on room air and temperature 37.8°C. You notice that Kal is alert, slightly pale compared to his parents and just doesn't quite look like the well babies you've seen. His cardiac exam reveals a systolic murmur and a hyperdynamic precordium. There are no signs of respiratory distress and the remaining respiratory exam is normal. His abdomen is soft and distended. His liver edge is non-palpable and his spleen tip is felt just below the costal margin. The initial investigations

were ordered by the ER doc and are back for your review with some critical results as you finish your history and physical. His CBCD shows a Hb 60 g/L, MCV: 50 fL, normal white cell and platelet counts as well as normal electrolytes and creatinine. Because of his age and CBC parameters, the lab automatically performed a peripheral blood smear which showed some hypochromic, microcytic red blood cells and anisopoikilocytosis with target cells. What could this mean? With this in mind let's explore beta thalassemias.

Beta genes are found on chromosome 11 and we inherit a single gene from each parent. Therefore, our genotypes consist of a total of two beta genes. Most commonly, beta thalassemia presents when there have been mutations of these genes. (2) The number of gene mutations and the type of variants present affect the phenotypic presentation of various beta thalassemias. In general, these phenotypes are as such:

Genotype	**Phenotype**
β/β^0 or β/β^+	Patients with one abnormal beta gene resulting in decreased beta globin production (and therefore decreased HbA) have beta thalassemia trait. Patients are asymptomatic and present with microcytosis. Their hemoglobin may be normal to slightly reduced.
β^+/β^+ or β^0/β^+	Patients with two beta gene mutations that allow for some residual beta globin production have beta thalassemia intermedia, a non-transfusion dependent beta thalassemia (NTDT). This is a spectrum of disease with variable clinical presentations depending on the patient's mutations. Patients can have clinically mild anemia to severe, symptomatic anemias that may require intermittent transfusions. Complications result from hemolysis, ineffective erythropoiesis, and iron overload.
β^0/β^0 or β^0/β^+	Patients with two beta gene mutations that result in zero or insufficient beta globin production have transfusion-dependent thalassemia (TDT). The patients generally present with severe anemia within the first year of life and require chronic red cell transfusions to sustain life. Complications from TDT are largely a result of transfusional iron overload.

As a note to the symbols: If you are looking at the transcript or PowerPoint, a superscript zero implies no beta globin production and a superscript plus means some beta globin is produced.

History and Physical Exam

Patients who have beta thalassemia trait are asymptomatic and have unremarkable physical exams. Patients with NTDT have a variety of symptoms and the severity of their presentation depends on their mutations and the resulting imbalance of alpha to beta globin. Patients with TDT are healthy at birth and tend to develop symptoms of anemia within the first year of life, usually around 6 months, as gamma globin production decreases and demand for beta globin production increases. If not diagnosed earlier, they can present with non-specific symptoms such as poor growth/failure to thrive, pallor, fatigue, poor feeding, dyspnea and irritability. Complications may include extramedullary hematopoiesis, pulmonary hypertension, thrombosis,

cholelithiasis, iron overload, poor growth, etc. On exam, there can be pallor, a hyperdynamic precordium and murmur, and mild to moderate hepatosplenomegaly depending on how low their Hb has dropped.

If an infant with TDT was detected and treated late, they may present with a prominent forehead and maxilla, bossing of the skull and/or long bone deformities with or without fractures. These boney physical exam findings are due to marrow expansion from high erythropoietic demand but are uncommon with early detection and intervention. (4, 6)

Investigations

The approach to investigations is similar to what we discussed for alpha thalassemia. First, we start with a CBC and peripheral blood smear. Those who have thalassemia trait would have reduced MCV and milder anisopoikilocytosis with microcytes and target cells. Basophilic stippling and nucleated red blood cells are typically absent. (6) In infants with TDT, laboratory investigations would demonstrate a severe, microcytic anemia with significant hypochromia, anisocytosis and poikilocytosis including target cells, basophilic stippling and nucleated red blood cells. The hemoglobin investigation would show increased HbA_2 and HbF with reduced or absent HbA.

Okay, let's go back to Kal who is waiting in the emergency. While you have been reading up on these findings, your staff has ordered 15mL/kg of packed red cells for Kal. What do you think is going on? How would you diagnose and manage him? You discuss with your staff and both agree that Kal likely has a thalassemia but to confirm the diagnosis hemoglobin investigations and subsequent molecular testing for beta globin mutations would need to be carried out and a referral to hematology for long-term management would be necessary.

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Two years later you are now a pediatric resident rotating through hematology and you are delighted to meet up with Kal again in clinic who was ultimately diagnosed with TDT. You have been reading up on how to manage thalassemia patients to prepare for this rotation…Let's see what you have come up with.

Thalassemia Management

Non-transfusion dependent thalassemia (NTDT)

As a reminder, this category typically includes: HbH disease, beta thalassemia intermedia and other hemoglobin variants. Complications result from hemolysis, ineffective erythropoiesis, as well as iron overload and may include extramedullary hematopoiesis, pulmonary hypertension, thrombosis, cholelithiasis, iron overload, poor growth, etc. If patients are growing normally, asymptomatic and the only finding is a mild, microcytic anemia they typically do not require any treatment other than folic acid supplementation as well as monitoring for potential complications. For more severe forms of NTDT, patients may require intermittent transfusions for symptomatic management. In general, NTDT has a wide spectrum of disease and treatment should be individualized. (6)

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Transfusion dependent thalassemia (TDT)

For beta thalassemia disease, patients are transfusion dependent, meaning that they need transfusions to sustain life. Because of the iron overload that ensues with chronic transfusions, patients also need daily, life-long iron chelation therapy. It is a combination of the TDT itself, iron overload from transfusions, and side effects of chelation therapy that contribute to the possible complications of this disease. These include iron overload cardiomyopathy, liver disease and endocrine pathologies (i.e. hypopituitarism, diabetes.) Iron chelation therapy is essential to minimize iron-related complications and patients are routinely monitored for iron overload of the heart and liver by MRI T2*. (6, 7)

Another management option in severe disease may include hematopoietic stem cell transplant (HSCT). This is a curative option and, if offered, should ideally be performed at a young age before complications of iron overload occur. (7) However, the risks and benefits of HSCT must be carefully weighed.

Take Home Points

Let's summarize the key information from these podcasts.

1. Keep thalassemia on the differential for a microcytic anemia as it is a frequent inherited hemoglobin disorder.
2. Thalassemia presentations can be variable and non-specific; therefore, a thorough history is important and should include a detailed family history including ethnicity and parental consanguinity.
3. Key features on physical exam in thalassemia diseases may include pallor, jaundice, failure to thrive, and hepatosplenomegaly but individuals with 'trait' status are asymptomatic.
4. Important investigations and findings for the work-up of thalassemia includes:
    - CBC showing low MCV, high RBCs, with or without decreased hemoglobin in trait and low MCV and variable Hb in disease, depending on its severity.
    - Peripheral blood smear showing hypochromic, microcytic, poikilocytosis with target cells, +/- nucleated red blood cells
    - Hemoglobinopathy investigations quantifying HbA, HbA_2 ,HbF and Hb variants
    - Genetic testing for beta or alpha globin genes, as appropriate
5. Thalassemia disease is sub-categorized into transfusion dependent and non-transfusion dependent thalassemia.
6. Management for TDT patients requires lifelong transfusions and iron chelation to prevent severe consequences of iron overload.

As this podcast concludes, we'd like to say thanks for listening and hopefully this will make you feel more confident diagnosing and managing thalassemia!

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