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APPROACH TO A PATIENT WITH SICKLE CELL DISEASE

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Hi, my name is Noha Elsherbini and I am a fourth year medical student at McGill University. This podcast has been created with Dr. Surabhi Rawal, Pediatric Hematologist Oncologist at the Montreal Children's Hospital in Montreal, Canada. This podcast will review the approach to Sickle Cell Disease, also known as Hemoglobin SS Disease, including pathophysiology, diagnosis, history, physical exam, investigations, and treatment.

The objectives of this podcast are to:

1. Describe the epidemiology of Sickle Cell Disease
2. Identify a major cause of mortality in children with Sickle Cell Disease
3. Explain how the diagnosis of Sickle Cell Disease is made
4. List key considerations for the history and physical exam in a patient with Sickle Cell Disease
5. Identify the main goals of treatment in Sickle Cell Disease

Introduction:

You are working in the Sickle Cell Disease Clinic and are about to see, Chloe, a 2-year-old girl with Sickle Cell Disease for her regular follow-up. In order to understand the impacts of Hemoglobin SS disease on Chloe, let us first review the pathophysiology of hemoglobin in Sickle Cell Disease.

Pathophysiology

Recall that the majority of Hemoglobin (Hb) in our body is HbA ($\alpha_2\beta_2$) which is composed of two alpha and two beta chains. Sickle Cell Disease is an autosomal recessive disorder caused by a mutation in the beta chain found on chromosome 11. If an individual only inherits one copy of this mutation, they are known to have sickle cell trait, and are generally asymptomatic. In fact, this mutation is carried by 10% of individuals of African descent likely because it confers protection against certain forms of malaria.

However, an individual who is homozygous for this mutation develops Sickle Cell Disease, also known as HbSS disease. Conditions including hypoxemia, dehydration, and acidosis cause HbSS to polymerize. These polymers damage red blood cell membranes causing them to sickle. Sickled red blood cells result in two major complications: hemolysis and vaso-occlusive crises.

Let's begin by discussing hemolysis. Hemolysis is the breakdown of red blood cells. It occurs when the mutated hemoglobin damages red blood cell membranes resulting in a normocytic anemia. This can manifest as fatigue, shortness of breath, and pallor. Lysing of red blood cells results in an unconjugated hyperbilirubinemia which clinically manifests as jaundice of the skin, mucosa and sclera of the eyes. High levels of bilirubin may also lead to bilirubin gallstone formation. Chronic hemolysis damages microvasculature and increases cardiac demand which may result in increased incidence of both systemic and pulmonary hypertension, chronic kidney disease, and cardiac disease in older individuals with HbSS disease. Sickle Cell Disease is a hemolytic anemia that is production-dependent to maintain a stable hemoglobin. When production is compromised by certain infections, notably parvovirus B19, patients can become very symptomatic.

Another main complication of sickled red blood cells are vaso-occlusive crises which are caused by ischemia secondary to the sickled cells clogging the microvasculature. These vaso-occlusive crises most often manifest as pain, however patients can develop hypovolemic shock or infarction such as in osteonecrosis, acute chest syndrome, and even stroke and can become functionally asplenic, leading them to increased risk of infection. Let's go through each of these.

1) Vaso-occlusive crises occur when sickled red blood cells obstruct small vessels. Crises can be extremely painful for the affected individual and may require admission and treatment with analgesia and hydration to alleviate symptoms. They can occur in various parts of the body, and most patients will experience painful episodes by the age of 6. Frequently, they effect the extremities such as in dactylitis which manifests as painful swollen hands and feet due to infarcts in the bones in children under 5 years old.

2) Patients with Sickle Cell Disease can become functionally asplenic because of chronic infarction of the spleen from sickled red blood cells. This increases the risk of infections with encapsulated organisms such as N. meningitides, H. influenza, Strep. Pneumonia, and Salmonella. Patients with HbSS disease are also more likely to develop salmonella osteomyelitis. In fact, sepsis is the most common cause of death in children with HbSS disease.

3) Hypovolemic shock can occur if the sickled red blood cells sequester into the splenic vasculature resulting in a precipitous drop in hemoglobin .

4) Infarction of various organs is another possible complication of vaso-occlusion. It may occur in the bones resulting in osteo-necrosis. If infarction happens in the pulmonary

circulation, this is called acute chest syndrome. It presents as a new pulmonary infiltrate on a chest x-ray accompanied by fever, chest pain, or respiratory distress. It is another major cause of mortality and accounts for 25% of deaths if not aggressively treated. Finally, children with HbSS are 300 times more likely to develop a stroke compared to other children. Acute chest syndrome and stroke are two major complications where exchange transfusion should be considered.

So now that we have reviewed the pathophysiology of Sickle Cell Disease, let us discuss how Chloe's diagnosis was made.

Diagnosis

HbSS disease is detected via hemoglobin electrophoresis. In Canada, only certain provinces and territories (Quebec, Ontario, British Columbia, New Brunswick, Nova Scotia, Prince Edward Island, and Yukon) have implemented universal newborn screening. Although it may be detected at birth, clinical manifestations do not typically appear before approximately 6 months of age. Children are not anemic at birth, nor will they have jaundice due to their Sickle Cell Disease. This is because infants have a high proportion of fetal hemoglobin (HbF) which is composed of two alpha, and two gamma chains. HbF binds more readily to oxygen which facilitates the transfer of oxygen from mom to baby in utero. The high proportion of HbF in infants results in a decreased amount of deoxygenated hemoglobin, and consequently less polymerization of hemoglobin and less sickling. As such, HbSS disease starts to manifest around 6 months of age as the percentage of HbF levels gradually declines after birth, and is replaced by mutated HbA containing the defective Beta chain.

Before you go see Chloe, you review her chart and note that she was diagnosed on newborn screen. You are now ready to go see Chloe and her mother. What should you be looking for on history and physical exam for Chloe's regular follow-up appointment?

Approach to the history

When approaching the history of a patient with known HbSS disease, you can start by taking a general pediatric history.

Next you can do a focused history to better understand the burden of the Sickle Cell Disease on the child. For example, has the patient ever required transfusions, or exchange transfusions? Have they ever had vaso-occlusive crises, in particular acute chest crisis or stroke? Did they require admission to the ward, or to the ICU? Have they had a splenectomy?

It is also important to inquire about medication adherence and to verify dosages. Common medications will be discussed in further detail in the treatment section, and include hydroxyurea, folic acid, amoxicillin or penicillin. In addition, it is important to ensure that vaccinations are up to date, and to verify routine imaging. This will also be discussed in the later sections.

Next, you can inquire about symptoms of HbSS including anemia, factors that could exacerbate sickling, signs of hemolysis, and pain episodes. Anemia can be elicited by asking about fatigue, shortness of breath, dizziness, and loss of consciousness.

You can ask about factors that may have triggered hypoxemic states and increased sickling such as recent illness (fever, cough, sick contacts), snoring, dehydration, extreme temperature changes, and recent air travel.

To inquire about increased hemolysis, ask about scleral icterus, jaundice of the skin, the mucosa, and darkening of the urine.

You should also inquire about pain such as dactylitis, limb pain, chest pain, headaches, abdominal pain, and priapism. Right upper quadrant pain may be due to gallstone formation. Flank pain with hematuria may indicate renal infarcts. Left upper quadrant pain may be due to splenic sequestration. Parents are often taught to palpate their child's spleen. It is important to note if the parent has recently found it to be larger than usual.

Finally, inquire about symptoms of end-organ injury. This includes respiratory symptoms (cough, shortness of breath, wheeze) as there can be airway hyper-reactivity associated with HbSS. Ask about nighttime enuresis, as it may be a symptom of cumulative renal injury resulting in a concentrating defect. Ask about visual disturbances, as retinal vasculature can be affected. A child with declining school performance may be having silent vaso-occlusive crises of the cerebral vasculature.

Chloe's mom tells you that she has been doing well. She has never had any admissions to the hospital, and never required any transfusions. She is taking her folic acid and daily antibiotics. Her vaccinations are up to date. Her mom tells you that recently she began to develop some swollen fingers and toes that seem to be causing her some pain. Her parents have previously declined Hydroxyurea treatment as Chloe had been doing so well and was asymptomatic but would like to discuss this during today's visit. Before you delve into this discussion, you ask to examine Chloe.

Approach to the physical exam

When examining a child with Sickle Cell Disease, it is important to first check their vitals. Any fever and decreased oxygen saturation should prompt a STAT chest x-ray to rule out an acute chest crisis or a pneumonia.

Next you can use a head-to-toe approach to perform a focused physical exam. Check the eyes for icterus, and the oral mucosa for pallor. Palpate the cervical lymph nodes. Auscultate the heart for a flow murmur. Auscultate the lungs for decreased air entry. Palpate the abdomen for hepatosplenomegaly. Examine the limbs for dactylitis or any other areas of bony pain.

On Chloe's exam, you note mild scleral icterus. You hear a flow murmur at the right sternal border. You did not feel any hepatosplenomegaly. You note however, her fingers and toes appear to be swollen and she withdraws when you try to touch them. Following this, you go check Chloe's laboratory results.

Investigations

1) Laboratory

At each visit, generally every 3 months, it is important to take note of certain lab values and trend them in order to assess the effectiveness of the treatment, and to monitor for adherence. Hb levels may be low but should be compensated by elevated reticulocyte count. Remember, patients with HbSS do not have a problem with production of the red blood cells, rather they have increased destruction of their red blood cells. As such, their bone marrow should compensate by increasing red blood cells count with reticulocytosis. The mean cell volume for untreated HbSS disease is normocytic. However, patients on hydroxyurea will have increased mean cell volume. Hydroxyurea also causes myelosuppression, so you may see the platelets and white blood cell count trending downward if treatment was recently initiated. Finally, hydroxyurea will increase the percent of HbF. Lab values such as liver enzymes and creatinine may also help determine the extent of end-organ damage. Hemolysis can be proxied by looking at the bilirubin level. If a patient is being chronically transfused, it is important to check the ferritin every 3 months.

You note that Chloe has a normocytic anemia with a hemoglobin of 75. Her reticulocyte count is appropriately elevated. Her bilirubin level has increased relative to the last visit. As a keen medical student, you also remember that patients with Sickle Cell Disease also require some special tests.

2) Special investigations

Transcranial Doppler ultrasound screening should be performed annually starting at age 2 to check for cerebrovascular disease. Increased flow velocity prompts prophylactic transfusion therapy. A child receiving chronic transfusion requires a liver and cardiac MRI to check for iron deposits every 6-12 months. At the age of 10 years, a baseline echocardiogram should be performed to evaluate for signs of pulmonary hypertension and repeated if there are new signs or symptoms of cardiac dysfunction. Moreover, starting at age 10, a full ophthalmologic exam should be performed every 1-2 years to evaluate for proliferative sickle retinopathy.

Chloe is 2 years old and is now due for her transcranial doppler. Now that we know what we should be monitoring, the next step is to determine the appropriate therapy for Chloe.

Treatment

The main treatment objectives in HbSS disease are to decrease sickling, reduce risk of infection, manage anemia, and control pain. It is important to recognize that many

lifestyle options can decrease sickling such as adequate hydration, avoiding extreme temperature change such as jumping in a cold pool on a warm day, and infection prevention.

1) Decrease sickling

Hydroxyurea is used to increase HbF concentrations thereby decreasing sickling. Treatment with hydroxyurea has been shown to improve overall survival by decreasing vaso-occlusive crises, need for transfusions, and improving cerebrovascular blood flow. It is indicated in patients after one episode of Acute Chest Syndrome. However, it can be started as early as 9 months of age. Early initiation of treatment decreases the long-term risk of complications from chronic inflammation of the vasculature such as pulmonary hypertension, systemic hypertension, and chronic kidney disease. In addition, increased hemoglobin decreases cardiovascular strain. One important side effect to be aware of is myelosuppression.

2) **Infection prevention**

Infection prevention is crucial since the most common cause of mortality in children with HbSS disease is sepsis. Children under 5 years old are given daily antibiotic prophylaxis with amoxicillin or penicillin because they are at a greater risk of developing infections from encapsulated organisms such as N. meningitides, H. influenza, S. Pneumonia, and Salmonella. Another important method to reduce risk of infection is through immunization. These children require vaccines that cover additional serotypes of meningococcus and streptococcus pneumonia that are not generally given to all children. In addition, asplenic patients travelling to regions where salmonella typhi is endemic should consider immunization.

3) Managing anemia

Patients with HbSS are generally placed on folic acid supplementation to aid in red blood cell turnover. If Hb levels dip below a patient's baseline, a transfusion of red blood cells can be given to treat the anemia. However, transfusion tends to be avoided if a patient has a good reticulocyte count and they are not hemodynamically unstable in order to avoid the risk of allo-immunization and iron overload.

4) Pain management

Pain management can be difficult in certain patients. Often, pain can be treated with acetaminophen and Ibuprofen. However, during acute vaso-occlusive pain crises, some children may require IV ketorolac, and IV opioids prompting an admission to the ward for proper pain control.

Acute chest syndrome and stroke are two major complications where exchange transfusion should be considered.

The only curative treatment for Sickle Cell Disease is via Hematopoietic Stem Cell Transplantation. This is generally offered to individuals with moderate to severe disease. Despite offering the potential for cure, Hematopoietic Stem Cell

Transplantation carries out long-term risks including gonadal failure and graft-versus-host disease. In addition, it is not always possible to find a matched HLA donor.

Case conclusion

Although Chloe has been relatively asymptomatic, she recently has developed symptoms of dactylitis. You explain the risks and benefits of hydroxyurea to Chloe's mom, and she agrees to begin treatment. In the meantime, you offer a prescription of acetaminophen to help with Chloe's painful dactylitis. You also give them a requisition to get the transcranial doppler and offer a follow-up appointment.

Summary

That brings us to the end of our podcast. Let's review the major points and the objectives:

Sickle Cell Disease is an autosomal recessive genetic mutation more commonly found in people of African descent. Sickled red blood cells result in hemolysis and vaso-occlusion leading to multiple complications. In certain Canadian provinces the diagnosis is made on newborn screening by hemoglobin electrophoresis. The primary cause of mortality is sepsis, and as such children are usually placed on prophylactic antibiotic therapy and need to have up to date vaccinations. Two major complications where exchange transfusion should be considered are acute chest syndrome and stroke. Treatment with hydroxyurea has been shown to improve overall survival and can be initiated as early as 9 months of age. Children with Sickle Cell Disease require regular long-term follow-up.

After listening to this podcast, you should now be able to:

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2. Identify a major cause of mortality in children with Sickle Cell Disease
3. Explain how the diagnosis of Sickle Cell Disease is made
4. List key considerations for the history and physical exam in a patient with Sickle Cell Disease
5. Name the main goals of treatment in Sickle Cell Disease

Thank you for listening!

Sources

Canadian Haemoglobinopathy Association Consensus Statement on the Care of Patients with Sickle Cell Disease in Canada Version 2 0 Ottawa; 2015

Borhade MB, Kondamudi NP. Sickle Cell Crisis. [Updated 2021 Feb 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526064/

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