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Hemolytic Anemia in Children

Developed by Prachi Shah and Dr. Aisha Bruce for PedsCases.com.
April 21, 2021

Introduction:

Hello everyone! My name is Prachi Shah and I am a medical student at the University of Alberta. This podcast on hemolytic anemia was made with guidance from Dr. Aisha Bruce, a pediatric hematologist at the Stollery Children's Hospital in Edmonton, Canada.

Objectives

By the end of this podcast, listeners should be able to:

1) Define hemolytic anemia and explain its pathophysiology
2) Describe the clinical manifestations of hemolytic anemia
3) List possible investigations to investigate hemolytic anemia
4) Outline the management of a child with hemolytic anemia

Case

Let's consider a possible scenario. You are working at a clinic when your preceptor asks you to go see a five year old boy named Robin. His parents are concerned about how pale he looks and say that his urine has turned a dark brownish red color. He also had a fever last week and again last night. Robin's diet is well balanced and his energy levels have been consistent, with a few tired days here and there in the last couple of months.

What would you like to ask them or do next?

Pathophysiology and Classification

Let's begin our discussion with the pathophysiology of hemolytic anemia, and some basic definitions. Anemia is a condition defined by a reduction in red blood cell mass or hemoglobin concentration. It presents in practice as a reduction of either/both hematocrit and hemoglobin[1].

Hemolytic anemia is a group of disorders where red blood cells are destroyed at a faster rate than they are produced. This can occur due to inherited or congenital causes. Inherited or congenital etiologies include[6]:

- Disorders where there is a change in the structure of hemoglobin (hemoglobinopathies), including sickle cell disease, thalassemias and unstable hemoglobins
- Red cell membrane defects which include hereditary spherocytosis, elliptocytosis, and others
- Enzyme deficiencies such as G6P dehydrogenase deficiency, pyruvate kinase deficiency and other glycolytic enzyme deficiencies

There are also acquired causes of hemolytic anemia, in which the red blood cells themselves are usually healthy but end up getting degraded in the circulation, or prematurely recycled in the spleen.

- Some acquired causes include: Infections, medications such as penicillin or sulfonamides, malignancies, and autoimmune disorders – lupus, Juvenile Idiopathic Arthritis, Ulcerative Colitis, Type I diabetes mellitus, and autoimmune thyroiditis. Hemolytic disease of the newborn, liver disease, and microangiopathies can also be causes although these would be accompanied by other findings.
- One type of acquired hemolytic anemia is autoimmune hemolytic anemia defined by the presence of autoantibodies that bind to and result in the premature destruction of one's red blood cells at a rate faster than the bone marrow is able to produce them. This condition can be isolated (primary) or due to systemic autoimmune conditions (secondary). It is further classified based on the temperature at which the autoantibodies are active. In warm-agglutinin disease the autoantibodies bind preferentially at 37C and accounts for 60-90% of cases. Cold-agglutinin disease is uncommon in children and accounts for roughly 10% of cases, most often occurring after Mycoplasma or EBV infection. Severe symptoms are more likely to occur in warm-agglutinin disease.

Clinical Presentation

Common signs and symptoms of anemia in a child are pallor, lethargy, and tachycardia[2]. In children, this may be brought to attention by parents concerned about lack of activity, drop in energy, and changes in school performance. Dark urine, scleral icterus, or jaundice can be indicative of a hemolytic disorder. Other symptoms include fever, abdominal or back pain, splenomegaly, hepatomegaly, and dizziness and confusion[3].

The symptoms of hemolytic anemia are relatively nonspecific and can look like other health problems[2]. It is important to have a suspicion of hemolytic anemia and ask probing questions in your history. Careful screening to rule out malignancy should also be done on history (including asking about constitutional symptoms such as fevers, night sweats, weight loss, as well as bony pain). Also ask around symptoms of other diseases on your differential diagnosis, such as hypothyroidism, inflammatory bowel disease, and liver disease.

It is important to ask questions related to bleeding including subtle bleeding. Occult bleeding causing anemia may require urgent treatment. Questions to ask for GI losses include changes in stool color, blood in stools, and any bowel symptoms. Epistaxis is frequent in children and may lead to anemia.

Past medical history should be obtained to determine if there are any underlying infectious or inflammatory conditions as these can result in anemia[2]. Any previous episodes of anemia should also be reviewed and characterized to include duration, etiology, therapy, and resolution. As well, enquire about previous episodes of any type of cytopenia (low platelets or white blood cells) that the child/family member may have experienced).

A review of current and past medications including any supplements is also important as oxidant drugs can cause hemolysis, especially in patients with G6PD deficiency. A dietary history focused on iron, folate, and B12 intake should also be done. For infants, info on type of diet, type of formula, and age at time of discontinuation of breast milk or formula should be obtained as well.

The pregnancy and birth history should include history of jaundice and/or anemia in the neonate period. Jaundice can occur, especially if hemolysis is rapid, due to the breakdown and recycling of unconjugated bilirubin from hemolyzed RBCs. All results of newborn screening should be reviewed, as this will typically include results of sickle cell disease screening.

In adolescent girls, a menstrual history is important, including duration and amount of bleeding, and any changes in menstruation.

To help determine if it is an inherited condition ensure to enquire about related symptoms that occur in those diseases such as relationship to episodes with exposure to medications or diet triggers (G6PD), pain or illness in sickle cell disease, and splenectomy in family members with hereditary spherocytosis. Previous cytopenias may be indicative of an underlying etiology (rheumatological) or an inherited marrow failure syndrome. Family history of anemia including inherited anemias, and asking if any members have undergone cholecystectomy or splenectomy should be included.

On physical exam, patient may appear fatigued and have pale pallor. Careful attention should be given to vital sign changes and level of activity/consciousness. A cardiac

examination usually shows tachycardia and an early systolic flow murmur. The presence of massive splenomegaly, hepatomegaly, or lymph node enlargement is suggestive of infection or malignancy and warrants further investigation. Further investigation is warranted if the physical exam is suggestive of any of the following: infection, malignancy, or autoimmune rheumatologic diseases.

Investigations

There are some standard investigations such as complete blood count, blood smear, and iron deficiency testing. Follow up investigations are done to determine and assess for the cause of the hemolytic anemia such as genetic testing, reticulocyte count, and liver enzymes.

CBC + differential is an essential test to diagnose anemia and assess for any other cytopenias. It is very helpful to compare to previous CBCs to determine trends and the chronicity of the issue. In a child with AIHA the degree of anemia may be surprising at initial evaluation. He/she may have hemoglobin concentration of 40-70 g/L with no cardiovascular compromise. RBC indices are not the best measure in AIHA since a normal MCV can actually be an average between small microspherocytes and large reticulocytes. The leukocyte and platelet counts should be within normal ranges.

Peripheral blood smear – viewing of red blood cells under the microscope can reveal findings consistent with hemolysis as well as some hemoglobinopathies (such as sickle cell anemia). RBC size, central pallor, and presence of fragmented cells are some of the notable findings consistent with hemolysis. In warm AIHA we often see small spherocytes due to splenic ingestion. It is common to see polychromasia in AIHA because the bone marrow releases high levels of reticulocytes and nucleated RBCs. Teardrop shapes and schistocytes are indicative of hemoglobinopathy or primary hepatic disease.

Reticulocyte count - reticulocytes are immature erythrocytes released from bone marrow. A high retic count can be indicative of hemolysis or blood loss leading to an increased erythropoietic response. A low retic count is suggestive of a decreased bone marrow response to anemia.

Suspicion of hemolytic anemia should include testing serum markers of hemolysis, in which overall trends in a patient would be elevated bilirubin and LDH, positive DAT, and low haptoglobin. Haptoglobin is not well synthesized in infants and is an acute phase reactant, and thus is not helpful in evaluating AIHA but can be used for older children[4]. Serum bilirubin levels higher than 85.5 umol/l are suggestive of hepatic impairment or Gilbert Syndrome[4]. A positive result of the DAT is highly suspicious of autoimmune hemolytic anemia.

Other helpful tests would be G6PD screening (but if there is a high clinical suspicion and the result is normal it may need to be repeated due to false negative results with

high reticulocyte counts) and a hemoglobin electrophoresis (thalassemia and sickle cell disease).

Testing for iron deficiency may include serum ferritin, iron, and total iron binding capacity. Testing serum folate, B12 and lead levels can help determine nutritional deficiencies and/or lead poisoning. A bone marrow aspirate or biopsy can be done if there is suspicion of leukemia or other marrow diseases.

Management

Your management of a child with hemolytic anemia will be dependent on the child's symptoms, age, and severity of condition. In children with AIHA, the severity and rapidity of how the anemia develops determines the treatment. A patient with mild anemia who has had recent viral illness can simply be observed. Therapy is required for cases of more severe anemia or if hemoglobin levels fall rapidly. Choice of therapy depends on the patient and type of anemia.

Autoimmune hemolytic anemia can occur quickly and the child's state may decompensate rapidly[4]. These patients require urgent treatment which should include careful consideration of admission, close observation, secure IV access and blood available (on hold) for the patient. Identification of compatible blood can be difficult due to the presence of antibodies; however, if the patient's clinical condition warrants transfusion it should not be withheld as it can be life-saving. Blood transfusion should be started at a slow rate and both plasma and urine need to be checked regularly for free hemoglobin. Close observation for transfusion reaction post transfusion is essential. For warm AIHA, patients are treated with corticosteroids (usually IV methylprednisolone) for 24-72 hours and then continue on oral prednisone for 2-4 months before tapering off[4]. Only ⅓ of patients with warm AIHA respond to IVIG therapy[5].

In all cases, these patients will require frequent blood tests and monitoring of hemoglobin level, reticulocyte count, bilirubin, LDH, and DAT. The frequency of monitoring will depend on the severity of the hemolytic anemia and the treatment. Steroids may be effective in certain cases however may mask underlying diagnosis such as malignancy, rheumatological disease, etc.

Long term therapy for children with autoimmune hemolytic anemia should include consultation with pediatric hematology[4]. Therapies such as rituximab, steroids and splenectomy may be potential options. Splenectomy has been shown to result in improvement in two-thirds of patients. Due to the risk of sepsis, this is avoided in children under 3 years old and not preferred until above 6 years of age. This option is not considered first-line therapy.

Case Resolution

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With all of that in mind, let's return to our case. After running lab tests and doing a physical exam, 5 year old Robin has been diagnosed with cold agglutinin autoimmune hemolytic anemia and is started on glucocorticoids. You counsel his parents that he will need regular follow-ups and that the benefits of glucocorticoid therapy outweigh any potential risks in Robin's case. He is admitted to hospital to have a full work up done and the hematology team is consulted.

Key Points and Conclusion

Let's summarize our key points:

1. Hemolytic anemia is a group of conditions defined by the destruction of red blood cells. They occur due to either inherited or acquired causes and present as a reduction in hemoglobin, hematocrit, or both.
2. Children with hemolytic anemia usually present with pallor, lethargy, and fatigue. Other indicators include darkened urine, scleral icterus, and jaundice. It is important to take a detailed history since the symptoms are relatively non-specific. Questions regarding bleeding, oncological, rheumatological (joint pain, rashes etc), menstruation, and the birth history are important.
3. CBC + differential, a blood smear, and reticulocyte count are essential in diagnosing hemolytic anemia. Some other important investigations are serum bilirubin, LDH, haptoglobin, and DAT.
4. Management of hemolytic anemia will be dependent on several factors. In emergency cases, a blood transfusion is given along with glucocorticoids. Antibiotics may be required if the cause is infectious. More rigorous treatment is needed in patients who don't respond to these measures and can include immunosuppressive therapy, splenectomy, etc.

To conclude, hemolytic anemias are a complex group of disorders in children and it is important for physicians to have a suspicion of diagnosis so as to not miss this condition. I hope this podcast served as a strong starting point or a refresher for you on this topic. Thank you to Dr. Bruce for her guidance and expertise, and thank you for listening!

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