Hemoglobin H Disease
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Hemoglobin H disease (HbH) is a form of alpha thalassemia in which moderately severe anemia develops due to reduced formation of alpha globin chains. In this condition, as in the other forms of thalassemia, there is an imbalance of globin chains needed to form hemoglobin. Normally, there are four genes to produce alpha globin chains. When three out of four of these genes become inactive, there are too few alpha globin chains to combine with beta chains and give rise to normal hemoglobin (hemoglobin A). The excess beta globin chains then combine with each other to form hemoglobin H, which is the origin of the name “hemoglobin H disease.”

While most individuals with HbH do not require transfusions, there is heterogeneity in the clinical course. This is an important component of the counseling for the family at the first clinic visit. HbH caused by deletion of three genes (deletional HbH) is less severe than cases in which two genes are deleted and the third gene has a point mutation (non-deletional HbH). HbH Constant Spring (HCS) is the most common form of non-deletional HbH in the United States.

In California, all newborns with HbH are identified through newborn screening, followed by identification of the alpha globin gene deletions or mutations by the Hemoglobin Reference Laboratory located at Children’s Hospital & Research Center Oakland. Older patients who are seen for the first time should have DNA testing to identify alpha globin gene deletions and the presence of the Constant Spring (CS) mutation. If only two alpha genes are deleted and the CS mutation is absent, further testing for uncommon mutations should be done. These patients should not be categorized as deletional HbH. Patients with HbH should also be screened for beta globin gene mutations with multiplex PCR. The complete genotype is used as the basis for discussion of a future clinical course and genetic counseling.

Routine Care
Patients should be seen frequently in the first year after diagnosis to establish hemoglobin level and monitor growth. Communication with the primary care provider is also important so that care can be coordinated. Later visits to a thalassemia center should occur once or twice a year, and routine health maintenance should be provided by the primary care provider. Patients with HCS should be followed closely by the thalassemia center because of the potential for severe anemia, growth delay, iron overload, and the need for splenectomy. All routine childhood vaccines should be completed and seasonal influenza vaccine given every year. All patients should receive folic acid, 0.5 to 1.0 mg per day.

Management of Fever
Owing to the risk of severe anemia during infections in HCS, such patients should be seen on the same day in the clinic or emergency room. Patients with deletional HbH can usually be seen in the clinic on the next day, unless an ER visit is warranted by the symptoms. A blood count with reticulocyte count and bilirubin level should be obtained. An admission for observation or transfusion may be needed if the hemoglobin has fallen below baseline. Antibiotic treatment is determined by assessing the source of infection. All splenectomized patients with fever should be seen on the same day and started on antibiotics (ceftriaxone is preferred). An admission is recommended until sepsis can be excluded. Oxidant drugs, which cause hemolysis in G6PD deficiency, should be avoided.

Splenectomy
Splenectomy is not required for deletional HbH disease. It may be required for patients with HCS when there are multiple episodes of sudden fall in hemoglobin level requiring transfusion, or if anemia is severe and affecting growth.

Transfusion Therapy
Common infectious diseases, such as common cold or viral fever, can lead to a rapid fall in hemoglobin level in HCS patients. The fall in hemoglobin level in HbH patients is much smaller, and the development of severe anemia needing transfusion is unlikely. Transfusions are given when hemoglobin falls below 6 g/dL. As mentioned above, splenectomy is recommended if there is a need for frequent transfusions. There is little role for chronic transfusion therapy such as that given to individuals with beta thalassemia major.

Iron Overload
Iron overload occurs in adults with HbH. In HCS, there is early iron overload that may need treatment. Patients’ ferritin and liver iron concentration should be monitored and measured via MRI or ferritometer.

Outreach
Patients should be provided with a card that shows the diagnosis and emergency contact number for their hematology service. Clinical summaries should be sent to the primary care provider with treatment recommendations. Families should be given a letter for school to explain the need for clinic visits. Children are allowed to determine their own limits of activity during physical education with no routine restrictions.
Adults with HbH

Genetic counseling is extremely important for adults. Ideally, a full testing of an adult patient’s partner for alpha and beta thalassemia mutations should be performed. At a minimum, testing for alpha thalassemia trait should be done to determine any risk for alpha thalassemia major which can be fatal to a fetus.

Patients with HbH who become pregnant should be monitored for further drop in hemoglobin level. Most of these patients will not need transfusions. Pregnant patients with HCS need close observation and should start regular transfusions if hemoglobin drops below 7 g/dL. Transfusions are performed every three to four weeks with the aim of maintaining pre- and post-transfusion hemoglobin levels at 9 and 12 g/dL, respectively.

All adults should have echocardiograms to screen for pulmonary hypertension, more frequently in those who are splenectomized. Older patients, particularly with HCS, should be evaluated for fatigue, difficulty in coping at work, and family stress.

Conclusions

Deletional HbH is asymptomatic during infancy and childhood, although deficits in growth may appear among older children. These individuals should receive all routine care through a primary care physician, with periodic evaluation by a hematology center. The key points are counseling the family and adopting strategies to avoid blood transfusion. In contrast, HCS is a potentially serious disease that needs close follow-up by a thalassemia specialty center to plan for emergency and elective transfusions, measure iron overload, monitor growth failure, and evaluate the need for splenectomy.