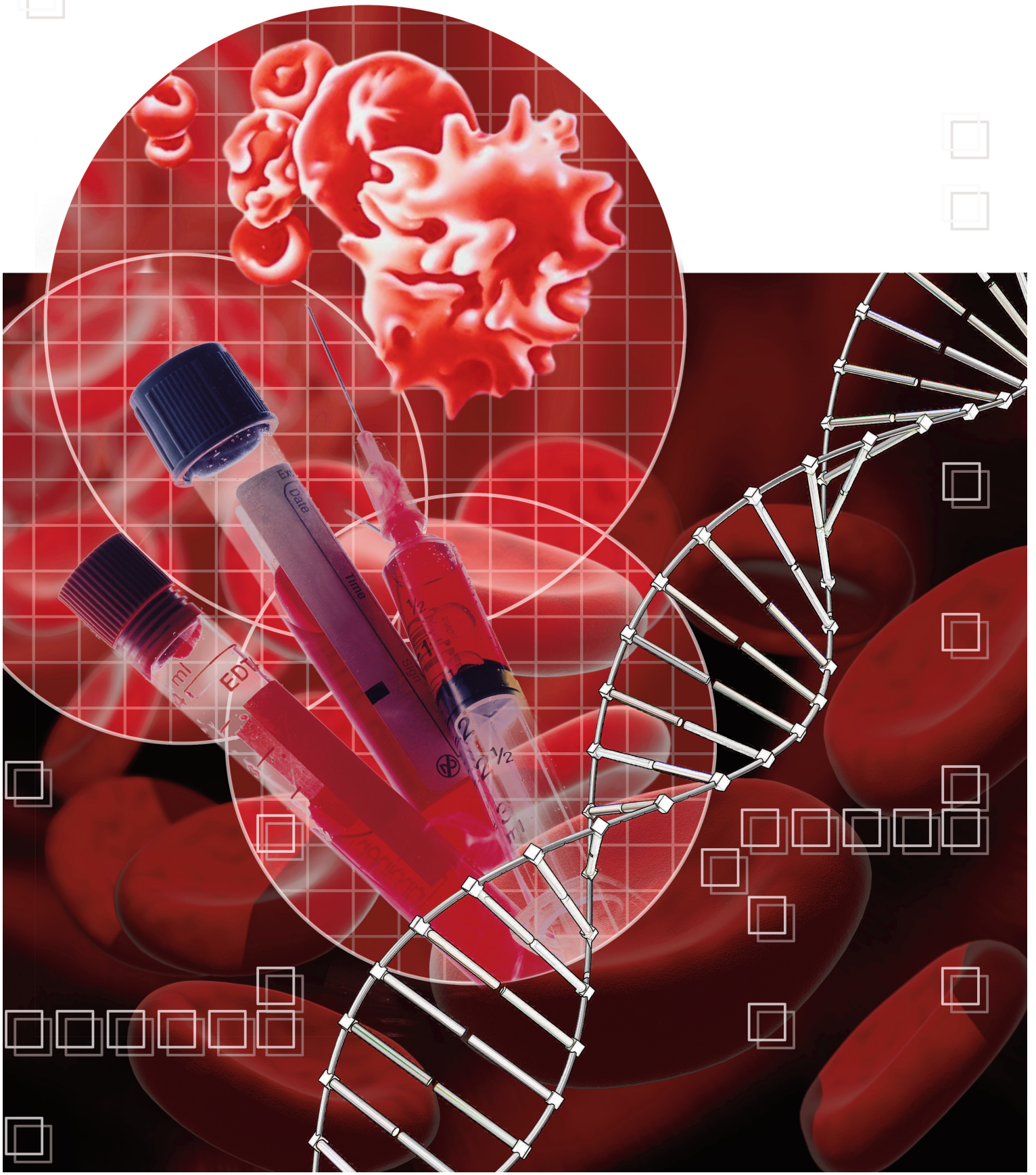

Date
Time
EDTA

CE 2.5 CONTACT HOURS

Thalassemia trait

What every NP should know

By Melissa Santiago, MSN, BA, PNP

A patient you are familiar with comes to your office complaining of moderate fatigue. On physical exam, you discover pallor. As part of your workup, you order a complete blood cell (CBC) count, which returns with a mild microcytic, hypochromic anemia. You know that the most common causes of microcytic anemia in children are irondeficiency anemia and the thalassemia traits. But what are the thalassemia traits? And how do you tell them apart from irondeficiency anemia?

The thalassemia syndromes are a heterogeneous group of inherited disorders of hemoglobin synthesis. They are a type of hemoglobinopathy and are disorders of decreased globin chain production. The term "thalassemia" is derived from the Greek root words for "anemia" and "sea" because the thalassemia syndromes were initially believed to be restricted to populations around the Mediterranean Sea.[1] Now recognized as a global health concern, the thalassemia syndromes are endemic to the Mediterranean region, the Middle East, India, Southeast Asia, Oceania, and sub-Saharan Africa.

The thalassemia syndromes are the most common genetic disorder of humans. Estimates of the number of hemoglobinopathy carriers may be as many as 270 million people worldwide.[2] Each year, it is estimated that there are 300,000 to 500,000 infants born with serious hemoglobinopathies, including serious thalassemias.

In the United States, there are currently about 100 million people whose ethnic backgrounds are high risk for carrier frequencies of the thalassemia syndromes.[2] The demography of people who are diagnosed in the United States with the thalassemia syndromes has changed over the years due to several factors. Declining immigration from the Mediterranean regions, improvements in therapy, and effective genetic counseling programs have resulted in a decline in pediatric thalassemic patients of Mediterranean heritage. Immigration from Asia, on the other hand, has increased and may be responsible for the increase in patients with thalassemia detected in newborn screening programs.[3] One lab that confirms thalassemia diagnoses contends that the thalassemia syndromes are far more diverse and prevalent in the United States than once thought. Their patients represent people of all ethnicities, some with no clear links to the areas of the world where the thalassemia syndromes are endemic.[4] It is estimated that in the United States, there are at least 2 million carriers for the thalassemia traits.[5]

The normal hemoglobin

Humans produce six different hemoglobin variants throughout their life cycles, three of which are usually only produced during fetal life. The hemoglobin molecule is typically formed by two pairs of globin chains with a heme compound joined to each chain. In most adults, 97% of the hemoglobin produced is hemoglobin A (HbA), which has two alpha-globin chains and two beta-globin chains. The remaining 2% to 3% of adult hemoglobin is hemoglobin A2, which is composed of a pair of alpha-globin chains and a pair of delta-globin chains. In some adults, fetal hemoglobin HbF, which is composed of two alpha- and two gamma-globins, may continue to be produced, but it does not typically exceed 2% of the hemoglobin production (see *Compositions of human hemoglobins* and *The normal hemoglobin molecule*).[6]

The genes that code for the globin chains are found on chromosomes 11 and 16. There are two genes on each chromosome 16 that code for alpha-globins, so most people have four genes that code for alpha-globin. Most people with normal hemoglobin have two beta-globin genes, one gene on each chromosome 11.[7]

Classification

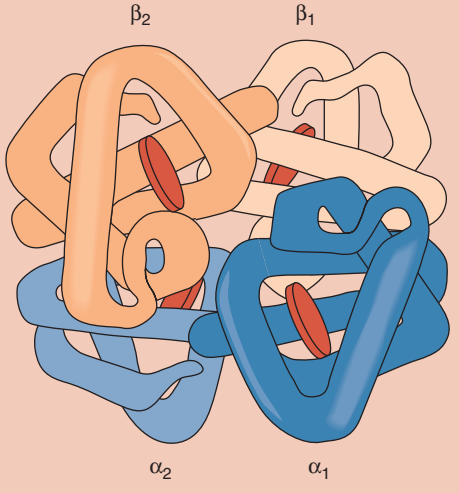
The thalassemias are classified according to the molecular basis of the globin chain deficit. If the deficiency is a result

Compositions of human hemoglobins

Type of hemoglobin	Composition	Comment
Fetal – F	α_2, γ_2 alpha-globin$_2$, gamma-globin$_2$	Normal hemoglobin
Adult – A	α_2, β_2 alpha-globin$_2$, beta-globin$_2$	Normal hemoglobin
Adult 2 – A2	α_2, δ_2 alpha-globin$_2$, delta-globin$_2$	Normal hemoglobin
Bart's	γ_4 gamma-globin$_4$	Abnormal hemoglobin
H	β_4 beta-globin$_4$	Abnormal hemoglobin

The normal hemoglobin molecule

This illustration represents the structure of the normal hemoglobin molecule, showing the four subunits.



of a mutation in the beta-globin gene, then it is beta-thalassemia. When one of the alpha-globin genes is mutated or absent, it is alpha-thalassemia.[1]

The thalassemias are also classified according to the form of the illness. Thalassemia major is severe and requires frequent blood transfusions for the patient to survive. Beta-thalassemia major is also known as Cooley's anemia and requires lifelong blood transfusions. Alpha-thalassemia major is also referred to as hydrops fetalis or hemoglobin Bart's hydrops syndrome, and often results in death.

Thalassemia intermedia is a term to describe patients with beta-thalassemia in whom the clinical severity falls between the minor and major forms. The major forms of thalassemia are out of the scope of this article. Instead, this discussion will cover the minor forms, which tend to be clinically mild, if not asymptomatic.[1]

Molecular basis of pathology

The alpha-thalassemias are among the most commonly inherited disorders in humans. There are a total of four alpha-globin genes, two genes per haploid genome. As a result, the descriptions of the alpha-thalassemias are based on the output of all four of the alpha-globin genes.[1]

There are two beta-globin genes controlling the production of beta-globin, one on each copy of chromosome 11. The beta-globin gene may have a mutation that results in the production of no beta-globin, noted as β^0, or it may have a mutation that results in reduced production of beta-globin, noted as β^+.[1] Beta-thalassemia trait occurs when a person acquires a normal beta-globin gene and a thalassemic beta-globin gene, or two thalassemic beta-globin genes that still produce minimal to moderate amounts of beta-globin chains (see *Possible genotypes of the thalassemia traits*).[8]

Pathophysiology

The thalassemia syndromes are a result of the deletion or mutation of one or more of the genes that code for the alpha-globin chains or the beta-globin chains, which causes an imbalance in the rates of globin-chain production. Normally, alpha- and beta-globin chains are produced at an identical rate. A mutated gene cannot produce as many globins as a nonmutated chain, resulting in a build-up of nonmutated gene chains within the cells and impaired hemoglobin production.[1]

Alpha-thalassemia

In alpha-thalassemia, there is an excess of the beta-globin chains, which form soluble tetramers, β_4, called hemoglobin H (HbH). In utero, there are also excess gamma-globins (γ- globins) that form tetramers, γ_4, called hemoglobin Barts (Hb Barts). In babies born with the alpha-thalassemia traits, it is possible to find Hb Barts and HbH in the cord blood, though they become undetectable during growth due to the transition from fetal type hemoglobins to adult types. Beta-globins no longer have to compete with the gamma-globins for available alpha-globin, so fewer HbH are created, and no Hb Barts are produced.[9]

In alpha-thalassemia, the creation of HbH is associated with the formation of Heinz bodies. The removal of these bodies results in the mechanical destruction of the red blood cell (RBC). Some of the other excess beta-globins become associated with RBC membranes. The association of beta-

Possible genotypes of the thalassemia traits

Type of alpha-thalassemia	Genotype	Alternative names
Normal genotype, no thalassemia	αα/αα	
Trait	αT/αT TT/αα α⁻/α⁻ – – /αα	Minor, or alpha-thalassemia-1 trait
Silent	α⁻/αα αT/αα	Minima or alpha-thalassemia-2 trait
Type of beta-thalassemia	**Genotype**	**Alternative names**
Normal genotype, no thalassemia	β/β	
Trait	β⁺/β β⁰/β	Minor

globins to the alpha-thalassemic RBC count results in increased cellular hydration and hyperstability. The heme groups associated with the beta-chains seem to become degraded and oxidized, resulting in damage to the membrane.[1]

Beta-thalassemia

Beta-thalassemia results from impaired production of the beta-globins, which leads to an excess accumulation of the alpha-globin chains. The extra alpha-globins precipitate and form inclusion bodies in the RBC, which may be apparent in most mild, beta-thalassemia traits.[9] The RBC in a patient with beta-thalassemia trait is more rigid and dehydrated than a normal RBC.[1]

Role of malaria

Due to similarities in the distributions of malaria and the thalassemias, it was hypothesized early on that the development of the heterozygous state of thalassemia, or the thalassemia traits, was positively selected for in the face of malarial infection. Alpha-thalassemia may offer some general protection against hospitalization from infectious diseases, specifically from severe malaria and anemia.[1,10,11] A recent study suggests that beta-thalassemic patients may be protected from malaria by an enhanced phagocytosis of the early intraerythrocytic form of malaria, called rings, in beta-thalassemic cells.[12]

Clinical manifestations

The thalassemia trait may be diagnosed as part of a family study, a population study, or an incidental finding during another illness. In other cases, the mild anemia may alert the healthcare provider during a routine visit. Thalassemia trait may be manifested by pallor, fatigue, or other nonspecific complaints associated with anemia. There may be a family history of anemia; often it has been mistakenly diagnosed as iron deficiency. The family's ethnic origin may be suggestive of a thalassemia trait if they are from the Mediterranean region, Africa, or Southeast Asia, but being of another ethnicity does not rule out a thalassemia trait. There is frequently a marked microcytosis, with a mean corpuscular volume (MCV) lower than normal for age, and mild to moderate hypochromia of the RBCs in alpha-thalassemia trait.[13] The characteristic RBC count index findings for beta-thalassemia trait are a high RBC count, mild anemia, and microcytic, hypochromic cells. Thus, the MCV and the mean corpuscular hemoglobin (MCH) are usually reduced, while the mean corpuscular hemoglobin concentration (MCHC) tends to remain in the normal range of values. Mild splenomegaly may be found in people with beta-thalassemia trait.[1] (see *Comparison of lab values in iron deficiency and thalassemia traits*).

Diagnosis

Diagnosing the thalassemia traits can be difficult because the lab values may mimic iron deficiency; there may even be concurrent iron deficiency. If anemia is found on a routine CBC, the first step is to check the MCV. If the MCV is below the expected range for age, further investigation should be initiated.[14] The Mentzer index (MI; MCV/RBC) may be a helpful screening tool in determining the next steps.[15,16] A MI over 13 is suggestive of an iron deficiency rather than a thalassemia trait. If a patient has a low MCV, a serum ferritin level should be obtained. However, if a patient has a low MCV and the MI is less than 13, this suggests a thalassemia trait, and a serum ferritin as well as a hemoglobin electrophoresis should be performed.

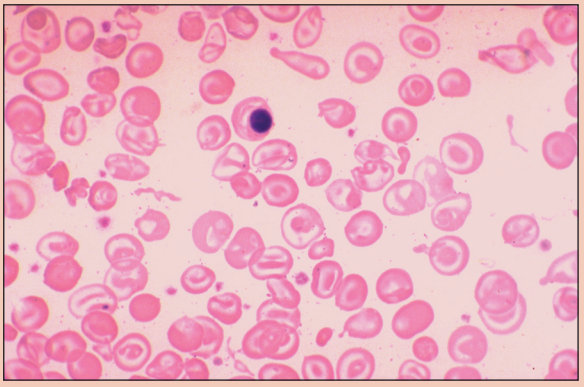
If the ferritin is low, the iron deficiency should be corrected, and the MCV reinterpreted afterward. If the ferritin is normal, a hemoglobin electrophoresis on cellulose acetate at a pH of 8.2 to 8.6 will identify hemoglobins A, F, and a number of other hemoglobin variants, along with the estimation of the HbA2 level. People with an elevated level of HbA2 along with hypochromic, microcytic RBCs have a beta-thalassemia trait (see *Peripheral blood erythrocytes in thalassemia*). If the HbA2 is borderline high to normal, it is likely that they have alpha-thalassemia or a combination of alpha-beta thalassemia.[1,17] Alpha-thalassemia trait is often regarded as a diagnosis of exclusion because the hemoglobin electrophoresis does not definitively prove it is an alpha-thalassemia trait. The definitive testing for alpha-thalassemia traits would be genetic testing that can determine the exact

Comparison of lab values in iron deficiency and thalassemia traits

	Iron deficiency	Beta thalassemia trait	Alpha thalassemia trait	Iron deficiency + thalassemia trait
MCV	Low	Low	Low	Low
RDW	High	Normal	Normal-high	High
RBC count number	Low	Normal-high	Normal-high	Normal-low
MI (MCV/RBC)	>13	<13	<13	<13
Ferritin	Low	Normal	Normal	Low
Transferrin saturation (serum iron/TIBC) x 100	Low	Normal	Normal	Low
Hemoglobin electrophoresis	Normal-low	Increased HbA2 (3.5%-7%), ±increased HbF	Normal	Low-normal
Response to iron therapy	Improves	No change	No change	Improves
Other		Presence of basophilic stippling on blood smear		

Peripheral blood erythrocytes in thalassemia

Blood smears will show hypochromic and microcytic erythrocytes in the patient with thalassemia.



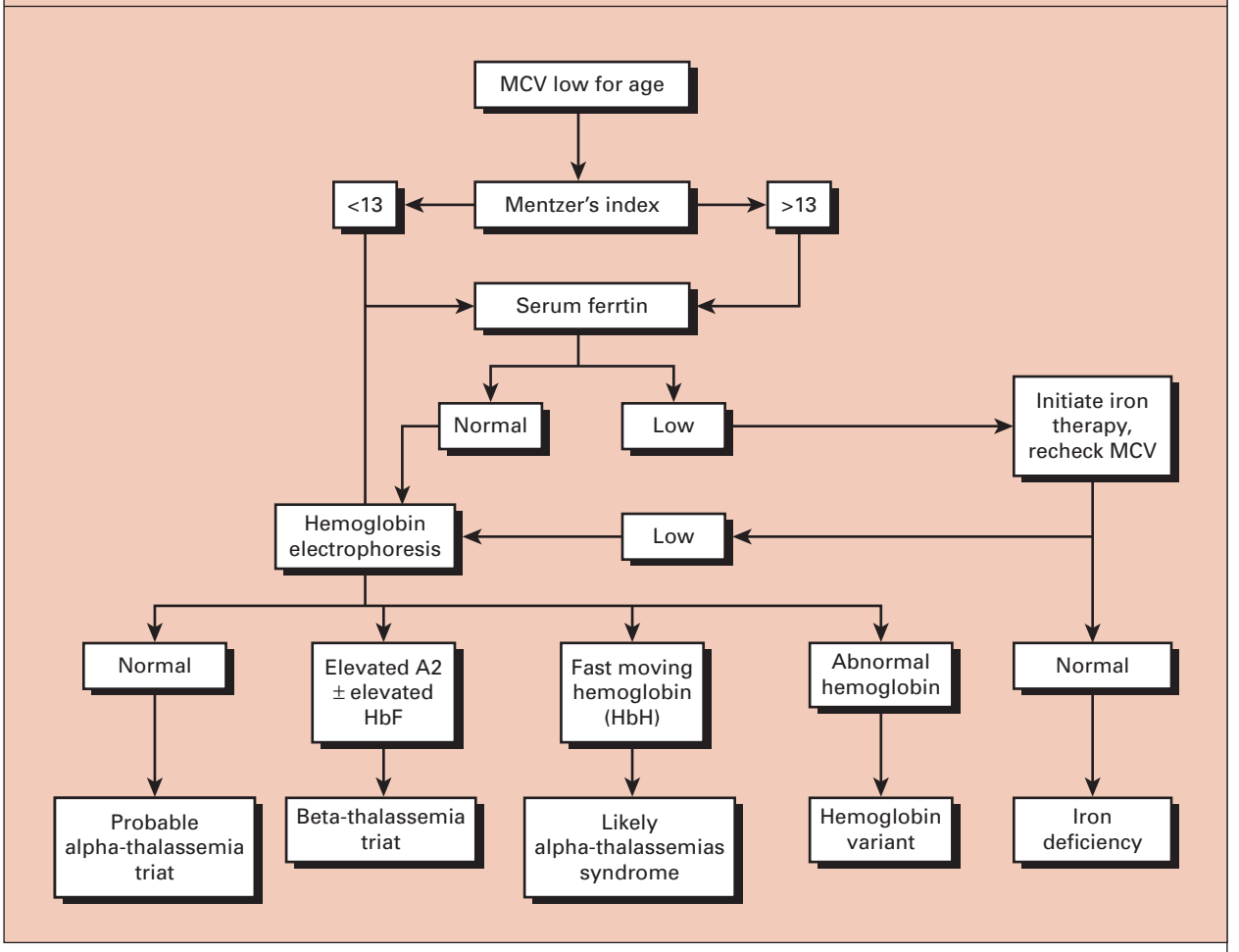
Source: Rubin R, Strayer D. eds. *Rubin's Pathology: Clinicopathologic Foundations of Medicine.* 5th ed. Philadelphia, PA: Wolters Kluwer/ Lippincott Williams & Wilkins; 2008:871.

number of deletions of the alpha-globin genes. These tests, however, are expensive.

If the MI is less than 13, a hemoglobin electrophoresis and serum ferritin study should be done together. Iron deficiency may obscure the results of the hemoglobin electrophoresis if thalassemia trait is present and may falsely normalize the results (see *Algorithm for diagnosing thalassemia traits*). Another consideration in the investigation of microcytic anemias are that lead poisoning may present as a microcytic anemia, so testing for lead exposure may be warranted. Anemia of chronic disease may also present as a microcytic anemia, although it more commonly presents as normocytic anemia. If anemia of chronic disease is suspected, a lab workup for inflammatory markers should be done.[16]

There have been several studies that attempted to assess the sensitivity and specificity of various RBC count indices to discriminate between iron deficiency anemia and the thalassemia traits. Each study has come to a different conclusion as to which index is the most accurate for elucidating the difference between the two anemias (see *Selected discriminatory RBC count indices)*. Several authors suggest the MI is suggested by several authors to determine the source of the anemias.[16–18] However, one study found that the England and Fraser (E&F) index had the highest sensitivity to differentiate between iron deficiency anemia and thalassemia.[19] A second study found the best index was the Green and King (G&K) index,[20] while a third found that the Shine and Lal, Srivastava, and MIs were all useful to discriminate between the anemias.[21] Thus, it is difficult to say with absolute certainty that any one of these indexes might be used for consistent, accurate diagnosis of thalassemia trait versus iron deficiency anemia. However, they appear to be useful in screening for thalassemia.

Algorithm for diagnosing thalassemia traits



Related health issues

Since the thalassemia traits are such a common, chronic condition, there are some specific health conditions to consider when managing these patients. Only one study so far has linked thalassemia trait with an increased risk of asthma.[22] Patients with the beta-thalassemia trait may be protected from hyperlipidemia. Several studies have documented that total cholesterol and low-density lipoprotein levels are significantly lower in those with beta-thalassemia traits than in the general population.[23,24] Although this may be beneficial, it may also predispose the patient to mood disorders. Lower rates of cholesterol seem to be linked to increased impulsiveness, so patients with thalassemic traits might be more likely to experience mood disorder.[24] There is a possible link between thalassemia traits and bipolar disorder.[25] A small study on beta-thalassemia trait as a risk factor of depression found no correlation among young adults, but the authors note that at older ages further study is needed.[26]

During pregnancy, the thalassemia traits are generally well tolerated. However, a few considerations must be made. In pregnant patients with beta-thalassemia trait, the hemoglobin may fall to a lower level versus patients without the trait. In cases where patients experience severe anemia, erythropoietin has been used successfully to increase erythropoiesis and fetal hemoglobin levels. A folic acid supplement should be given to women with beta-thalassemia trait because beta-thalassemia trait can create a slight folic acid deficiency due to the increased erythpoiesis.[7] Pregnant patients with beta-thalassemia minor may also be at risk for experiencing intrauterine growth retardation, so these patients should be monitored closely for early detection of the condition.[27]

It may be advisable to educate parents of children with thalassemia minor that a transient aplastic crisis is a possible complication of parvovirus infection, since the patient may have a decrease in erythrocytes.[28] Parvovirus causes an aplasia of the RBC for 7 to 10 days that rarely causes a

Selected discriminatory RBC count indices

Formula name	Formula	Value favoring thalassemia	Value favoring iron deficiency
RBC	RBC count value	>5	<5
Red cell distribution width (RDW)	RDW value	<14	>14
RDW index	MCV x (RDW/RBC)	<220	>220
Mentzer index (MI)	MCV/RBC	<13	>13
Shine and Lal index (S&L)	$(MCV)^2$ x MCH x 0.01	<1,530	>1,530
Srivastava index (SI)	MCH/RBC	<4.4	>4.4
Ricerca index (RI)	RDW/RBC	<3.3	>3.3
E&F index	MCV – RBC – (Hb x 5) - *k* *k* is a constant determined by the method used to calibrate the Coulter counter	<0	>0
G&K index	$([MCV]^2$ x RDW)/(Hb x 100)	<72	>72

problem in patients without a hemoglobinopathy. There have been a few cases of transient aplastic anemia associated with thalassemia minor and infection with parvovirus B19.[1]

Role of the NP

The NP's role in providing care to patients with thalassemia trait is multifaceted. The first is the prompt recognition and careful diagnosis of the trait. It is important to differentiate between thalassemia and irondeficiency anemia to avoid unnecessary iron supplementation. However, irondeficiency anemia may also occur with the thalassemia, confounding the issue. The NP must correctly interpret the results of a CBC and use one of the indexes discussed when microcytosis is found. Evaluation of the RDW and iron studies may need to be performed to differentiate between the two or to find concurrent thalassemia trait and irondeficiency anemia.

It is also important for NPs to properly interpret the results of a newborn screening. Newborn screening for sickle cell disease is required in nearly every state, and a hemoglobin variant may be picked up incidentally on the newborn screening.[29] This is particularly critical for the diagnosis of alpha-thalassemia trait, as Bart's hemoglobin may be transiently detected in the cord or newborn blood, but disappears rapidly as the newborn transitions to mainly adult-type hemoglobin.[30]

Diagnosis must be followed by counseling the family. If a family presents with a child with beta-thalassemia, it is likely that at least one parent has the trait as well. If both parents have the trait, it is highly likely that any future children will have a major thalassemia syndrome. It is therefore up to the NP to become familiar with the disorders and provide patient education and counseling about genetic testing for these traits. The NP should also be familiar with specialists for referral if the parents decide to explore genetic counseling.[31]

The NP may also play a vital role in stimulating awareness of the need for more research into the thalassemia traits. Much research into the thalassemias in the past has focused on the major types, and comparatively little research has been done with the thalassemia traits. Because the hemodynamics of a patient with thalassemia trait may be slightly altered, a variety of other systems may be affected. More research is needed to conclusively say whether or not the thalassemia traits are associated with any other illnesses or if they offer protective factors against other illnesses. NP

REFERENCES

1. Weatherall DJ. *The Thalassemia Syndromes.* 4th ed. Oxford: Malden, MA: Blackwell Science; 2001.
2. Chui DHK, Cunningham MJ, Luo H, Wolfe LC, Neufeld E J, Steinberg MH. Screening and counseling for thalassemia. *Blood.* 2006;107(4):1735-1737.
3. Vichinsky EP, MacKlin EA, Waye JS, Lorey F, Olivieri NF. Changes in the epidemiology of thalassemia in North America: a new minority disease. *Pediatrics.* 2005;116(6):e818-e825.
4. Luo H-y, Boudreaux J, Steinberg MH, Chui DHK. Patients with thalassemia in the United States. *Blood.* 2005;105(12):4896-4897.
5. Northern California Comprehensive Thalassemia Center. Thalassemia trait. http://www.thalassemia.com/thal_trait.html.
6. Steinberg MH, Benz EJ. Pathobiology of the human erythrocyte and its hemoglobins. In: RL Hoffman, ed. *Hematology: Basic Principles and Practice.* 4th ed. Philadelphia, PA: Churchilll Livingstone; 2005:356-371.
7. Rappaport VJ, Velazquez M, Williams K. Hemoglobinopathies in pregnancy. *Obstet Gynecol Clin N Am.* 2004;31(2):287-317.
8. Birgens H, Ljung R. The thalassaemia syndromes. *Scand J Clin Lab Invest.* 2007;67(1):11-26.

9. Thien SL. Genetic insights into the clinical diversity of beta-thalassemia. *Br J Haematol.* 2004;124:264-274.
10. Mockenhaupt FP, Ehrhardt S, Gellert S, et al. Alpha+-thalassemia protects African children from severe malaria. *Blood.* 2004;104(7):2003-2006.
11. Wambua S, Mwangi TW, Kortok M, et al. The effect of alpha +-thalassaemia on the incidence of malaria and other diseases in children living on the coast of Kenya. *PLoS Med.* 2006;3(5):e158.
12. Ayi K, Turrini F, Piga A, Arese P. Enhanced phagocytosis of ring-parasitized mutant erythrocytes: a common mechanism that may explain protection against falciparum malaria in sickle trait and beta-thalassemia trait. *Blood.* 2004;104(10): 3364-3371.
13. Forget BG. Thalassemia syndromes. In RL Hoffman, ed. *Hematology: Basic Principles and Practice.* 4th ed. Philadelphia: Churchilll Livingstone; 2005:485-509.
14. Sirichotiyakul S, Maneerat J, Sa-nguansermsri T, Dhananjayanonda P, Tongsong T. Sensitivity and specificity of mean corpuscular volume testing for screening for alpha-thalassemia-1 and beta-thalassemia traits. *J Obstet Gynaecol Res.* 2005;31(3):198-201.
15. Hermiston ML, Mentzer WC. A practical approach to the evaluation of the anemic child. *Pediatr Clin N Am.* 2002;49:877-891.
16. Richardson M. Microcytic anemia. *Pediatr Rev.* 2007;28:5-14.
17. Segel GB, Hirsh MG, Feig SA. Managing anemia in pediatric office practice: part 1. *Pediatr Rev.* 2002;23(3):75-84.
18. Swartz MK. Hematologic diseases. In Burns CE, Dunn AM, Brady MA, Starr NB, Blosser CG,eds. *Pediatric Primary Care: A Handbook for Nurse Practitioners.* 4th ed. St. Louis, MO: Saunders; 2004:612-632
19. AlFadhli SM, Al-Awadhi AM, AlKhaldi Da. Validity assessment of nine discriminant functions used for the differentiation between iron deficiency anemia and thalassemia minor. *J Trop Pediatr.* 2007; 53(2):93-97.
20. Ntaios G, Chatzinikolaou A, Saouli Z, et al. Discrimination indices as screening tests for beta-thalassemic trait. *Ann Hematol.* 2007;86(7):487-491.
21. Rathod DA, Kaur A, Patel V, et al. Usefulness of cell counter-based parameters and formulas in detection of beta-thalassemia trait in areas of high prevalence. *Am J Clin Pathol.* 2007;128:585-589.
22. Palma-Carlos L, Palma-Carlos AG, Costa AC. "Minor" hemoglobinopathies: a risk factor for asthma. *Allergie et immunologie.* 2005;37(5):177-182.
23. Karimi M, Marvasti VE, Motazedian S, Sharifian M. Is beta-thalassemia trait a protective factor against hypertension in young adults? *Ann Hematol.* 2006;85:29-31.
24. Namazi MR. Minor thalassemias may be a risk factor for impulsiveness. *Med Hypotheses.* 2003;60(3):335-336.
25. Bocchetta A. Heterozygous beta-thalassemia as a susceptibility factor in mood disorders: excessive prevalence in bipolar patients. *Clin Pract Epidemiol Mental Health.* 2005;1(1):6.
26. Marvasti VE, Dastoori P, Karimi M. Is beta-thalassemia trait a risk factor for developing depression in young adults? *Ann Hematol.* 2006;85:873-874.
27. Sheiner EMD, Levy AP, Yerushalmi RMD, Katz MMD. (2004). Beta-thalassemia minor during pregnancy. *Obstet Gynecol.* 2004;103(6):1273-1277.
28. Servey JT, Reamy BV, Hodge J. Clinical presentations of parvovirus B19. *Am Fam Physician.* 2007;75(3):373-376.
29. National Newborn Screening and Genetics Resource Center. National Newborn Screening Status Report—State Disorder List; 2008. http://genes-r-us.uthscsa.edu/nbsdisorders.htm.
30. Cunningham MJ. Update on thalassemia: clinical care and complications. *Pediatr Clin N Am.* 2008;55:447-460.
31. Cheng TL, Cohn RD, Dover GJ. The genetics revolution and primary care pediatrics. *J Am Med Assoc.* 2008;299(4):451-453.

ACKNOWLEDGMENT

The author gratefully acknowledges the assistance of Dr. Ritamarie John of Columbia University's School of Nursing for all her encouragement and assistance in the creation of this article.

The author has disclosed that she has no significant relationship or financial interest in any commercial companies that pertain to this educational activity.

Melissa Santiago is a pediatric nurse practitioner at the Columbia School of Nursing, New York, N.Y.