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Genetic blood disorders: Questions you need to ask

No one is better positioned than you to look for evidence of inherited diseases—especially when you consider that many FPs care for 2, or even 3, generations of a single family.

PRACTICE RECOMMENDATIONS

› *Advise patients at risk for genetic disorders to be tested before starting a family, as carrier status identified at birth is often lost to follow up.* (C)

› *Keep genetic blood disorders in mind for patients of all ages; the most common form of porphyria, as well as hereditary hemochromatosis, often remains hidden until well into adulthood.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence
(B) Inconsistent or limited-quality patient-oriented evidence
(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Some inherited diseases are found as a result of routine neonatal screening. Others remain hidden for years—until a pregnant woman is tested, an older patient receives a particular laboratory test, or signs and symptoms of a previously undetected disorder emerge.

To recognize the signs and respond appropriately, you need to know which patient populations are at heightened risk for which inherited diseases. It is crucial, too, to routinely obtain a comprehensive medical history.

General questions about the health status of family members may be sufficient when there is no reason to suspect a genetic disease. When you have evidence or a reasonable suspicion of a particular disorder, however, a targeted family history (**TABLE**) is essential. It is crucial, too, to thoroughly document any evidence of an inherited condition found at birth, as well as to advise patients of reproductive age who may be carriers to seek genetic testing or counseling when they begin thinking about starting a family. This review focuses on inherited blood disorders, but these principles apply to other genetic diseases, as well.

Sickle cell disease

About one in 500 African Americans are born with sickle cell disease (SCD)—perhaps the best-known inherited blood disorder. Far more (approximately one in 12) are carriers. SCD also affects people of Hispanic origin, although the incidence (about one in 36,000) is much lower than that of blacks. Overall, an estimated 70,000 to 100,000 US residents have SCD.[1,2]

Inheritance

The genetics of SCD are fairly straightforward: A mutation

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in the hemoglobin beta chain results in a single amino acid substitution of the normal glutamic acid.[3] The mode of inheritance is autosomal recessive. Simply put, patients with SCD have 2 abnormal genes (one from each parent) that cause their red blood cells to change shape. People with sickle cell trait have only one abnormal gene. They cannot develop SCD themselves, but they are carriers of the disease.

Testing

SCD is typically diagnosed as a result of routine neonatal screening (screening newborns for SCD is mandatory in every state).[4] The gold standard test is hemoglobin electrophoresis. Although gene sequencing can be used to distinguish SCD from other hemoglobinopathies in equivocal cases, this is rarely necessary.[5]

Clinical presentation

Infants with SCD are typically asymptomatic for the first few months of life. This is because of the persistence of fetal hemoglobin, which is not predisposed to sickling.[6]

In many cases, hand/mouth syndrome—a painful swelling of the hands and feet—is the first physical manifestation of SCD and is treated with pain medication and an increase in fluids. The clinical course of SCD, although somewhat variable, is characterized by sickle cell and pain crises.

Sickle cell crisis occurs when a precipitating factor, such as a temperature change, dehydration, or infection, induces the abnormal genes to polymerize and deform the red blood cells, which then hemolyze. Microinfarctions can occur throughout the body, causing intense pain. The hematocrit may fall precipitously. If the bone marrow is unable to replace the hemolyzed red blood cells, an aplastic crisis may result.

A pain crisis is similar, with one key difference: Hematocrit levels do not drop precipitously. It is not always possible to distinguish between a sickle cell crisis and a pain crisis within the first few hours of presentation. However, prompt recognition and rapid treatment of an acute flare-up (with analgesia, oxygen, hydration, and a search for the precipitating cause) can sometimes prevent the drop in hematocrit associated with a sickle cell crisis.[7]

Treatment and follow-up

A rapid response to flare-ups is a key reason

TABLE

Family history as a guide to genetic disease

General (ask all patients)
Are your parents alive?
- If so, how old are they? What is the status of their health?
- If not, what did they die of, and at what age?
Do you have any siblings?
- If so, what are their ages and the status of their health?
- If they are deceased, what caused their death and at what age?
Are there any diseases that run in your family (eg, breast or colon cancer, heart disease, type 2 diabetes, or genetic disorders)?
Targeted family history (tailored to diagnosis or suspected disorder)
Has anyone else in your family had this disease?
Has anyone in the family:
- required frequent blood transfusions?
- donated blood or been told by a doctor to give blood frequently?
- been extremely sensitive to the sun?
- had a bronzed appearance not related to sun exposure or purposeful tanning?
Family/social history
Who is living in the home with you (or your child)?
Are there any children who may be affected or may be silent carriers?
Would you be willing to see a genetic counselor?

Bone marrow transplantation offers hope for patients with sickle cell disease and other potentially fatal inherited blood disorders.

for primary care physicians and patients with SCD (or their parents) to develop a close relationship. Physicians caring for such patients must ensure that they receive adequate pain management, control of sickling events, and, when necessary, access to emergency services without delay. Blood transfusions are needed to treat severe anemia, which may develop as a result of an infection or enlargement of the spleen.

Beyond the crisis. Management of SCD involves more than responding to crises. Magnesium, taken regularly, can stabilize red cell membranes, and hydroxyurea, which increases fetal hemoglobin, may reduce the frequency of attacks.[8] Screening for folate and B12 deficiency should be considered prior to supplementation.[9] Bone marrow transplantation and gene therapy are being explored, as well.[10]

Growing awareness of SCD and improvements in disease management have extended the life expectancy of patients with the disease in recent years to the mid-40s, on average.[11] Advances in our understanding of SCD, however, have done little to reduce the incidence of the disease.[6]

Part of the problem is that sickle cell trait—like carrier status of other genetic diseases identified at birth—is often forgotten or overlooked by the time the patient reaches reproductive age. Family physicians can help by educating parents of a newborn with an SCD diagnosis—or with sickle cell trait—about the risks of passing on the disorder. It is equally important to advise teens and young adults to find out whether they or their partners are carriers, stressing the need for both parties to be tested before they marry or start a family.

Thalassemia

Originally described by Thomas Cooley in 1925,[12] thalassemia is named for the Greek

word for sea (thalassa)—reflecting the fact that for many years, those most affected lived in the vicinity of the Mediterranean Sea.[13] Unlike SCD, which is caused by a qualitative problem involving the beta chain of hemoglobin, thalassemia is characterized by quantitative defects in the synthesis of either the alpha or beta hemoglobin chain.

Thus, thalassemia is a spectrum disorder designated in part by the chain of hemoglobin (alpha or beta) that is affected. The *HbVar Database of Human Hemoglobin Variants and Thalassemia Mutations* (http://globin.bx.psu.edu/hbvar/) lists hundreds of mutations associated with various subtypes, with particular forms of the disease found in certain ethnic groups.

The number of Americans affected by thalassemia is not known. It is estimated, however, that 15% of African Americans (the US population with the highest incidence of any form of thalassemia) are affected by alpha thalassemia.[14] The incidence of beta thalassemia among Mediterranean, African, and Middle Eastern populations ranges from about 5% to 25%.[15]

Inheritance

Most people have 4 genes for the alpha chain of hemoglobin (2 from each parent) and 2 genes for the beta chain of hemoglobin (one maternal and one paternal). The severity of the disorder typically depends on the number of genes affected.

Individuals in which one alpha gene is missing or damaged are silent carriers, while those with 2 affected genes may have a subclinical anemia, often mistaken for iron deficiency anemia. Those in which 3 alpha genes are missing or defective have hemoglobin H disease, a serious condition that causes an enlarged liver and spleen and hemolytic anemia. When all 4 alpha genes are affected, the result is hydrops fetalis, a condition that leads to the death of the fetus or newborn.[16]

Beta thalassemia—the group of disorders caused by reduced or absent synthesis of the beta chains of hemoglobin—is further classified as minor, intermediate, or major (also known as Cooley's anemia). People with minor beta thalassemia are typically asymptomatic; those with major thalassemia are severely affected, and often die by the age of 20 years.[17]

Testing

Routine neonatal screening can detect both alpha and beta thalassemia and identify asymptomatic carriers. Confirmation testing is widely available by hemoglobin electrophoresis. Antenatal testing can be performed via amniocentesis or chorionic villus sampling, and is indicated in countries in which thalassemia is relatively prevalent. In the United States, we typically take a family history and may screen the parents for carrier status.[18]

Clinical presentation

Mild forms of thalassemia are often mistaken for iron deficiency anemia, and it is likely that the prevalence of this inherited disease is underestimated.[19] Patients at the intermediate level often need transfusions under circumstances in which they're not typically required, such as childbirth. Those with thalassemia major develop splenomegaly and bone malformations. Although patients with thalassemia major have not been expected to live much beyond adulthood, the disorder has been treated successfully with bone marrow transplantation in recent years.[20]

Treatment and follow-up

Patients who are severely affected by thalassemia need frequent transfusions; ensuring that they receive emergency services, as needed, is key. When caring for such patients—or for individuals who have symptoms suggestive of thalassemia or whose children are found to be carriers—targeted questions about family medical history are necessary, as well. Asking whether anyone in the family has required blood transfusions or had "problems with their blood" may help you detect patterns suggestive of a family history of thalassemia.

As is the case with sickle cell trait, however, the significance (or evidence) of carrier status may be lost by the time a child reaches reproductive age. Thus, the medical records of patients found to be carriers of any genetic disorder should be flagged, and individuals from affected racial/ethnic groups should be routinely advised to review their own and

The prevalence of thalassemia may be underestimated, as mild forms are often misdiagnosed as iron deficiency anemia.

FIGURE

Erythropoietic porphyria: Distinguishing characteristics

PHOTOS COURTESY OF: SUDIP KUMAR GHOSH, MD, DNB, DDERMAT

Patients with erythropoietic porphyria, like the one shown here, often present with reddish coloration of the teeth and red urine.

their partner's genetic status as part of the family planning process. Parents who fail to consider carrier status may have children who inherit SCD, thalassemia, or a combination of these diseases.[21,22]

Porphyria

Porphyria may encompass an even wider spectrum of disorders than thalassemia. The various clinical entities have little in common other than their pathophysiology—disordered heme synthesis. As heme is synthesized, it transitions through several highly reactive states, and deficiencies in different areas result in different syndromes. When there is a deficiency in one of the enzymes in the heme degradation pathway, reactive metabolites upstream of the defect may occur.

However, all porphyrias have one common feature: the accumulation of porphyrins or their precursors, which sometimes gives the urine a reddish color. A number of porphyrias are extremely rare—only 5 cases of dehydrogenase deficiency porphyria have been reported,for example, and the incidence of congenital erythropoietic porphyria is <1 in a million.[23,24]

Others occur a bit more frequently in particular ethnic groups. Variegate porphyria, a hepatic form of the disorder associated with acute attacks and photosensitivity, is particularly common among the white South African population, for example.[25] Among Eastern Europeans, the incidence of porphyria cutanea tarda (PCT)—the most common porphyria—may be as high as 1 in 5000.[25] The "tarda" in the name reflects the fact that, unlike other porphyrias, onset of PCT occurs later in life.[26]

Inheritance

Inheritance varies by condition. PCT is autosomal dominant, as are most porphyrias; acute intermittent porphyria, however, is autosomal recessive. Some cases of PCT are acquired, occurring as a result of exposure to environmental or infectious agents.[27]

Testing

A random urine porphobilinogen (PBG) is a useful screening test for porphyria, although checking urine for fluorescence may be the most readily available clinical examination. Further delineation using urine and fecal porphyrins is usually not readily available, and may require sending specimens to a specialized laboratory. "GeneReviews" (http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=GeneTests) is a useful resource for locating such labs; the site also provides educational material about genetic diseases as well as information about specimen collection and billing.

Clinical presentation

Characterized by irritable and erratic behavior provoked by sunlight (with varying degrees of hirsutism) and ameliorated by ingesting fresh blood, porphyria could have been the inspiration for the vampire legends.[28] Although symptoms vary from one type of porphyria to another, most affect either the nervous system or the skin. Some

A case for phlebotomized blood

The problem is straightforward: The United States has a shortage of donor blood, and phlebotomized blood from patients with hereditary hemochromatosis (HH) is available in large quantities—and is an excellent source of blood for patients with severe anemia. Yet blood banks often discard it.[39]

Sweden has used phlebotomies as a source of donor blood since 1984, with no ill effects.[40] Until 1999, US blood banks were permitted to use blood from patients with HH, provided they indicated on the label that it came from a patient with the disorder. Since then, the US Food and Drug Administration (FDA) has permitted blood banks to apply for a variance permitting them to use this blood without labeling it as such. The standard safety measures apply to the phlebotomized blood, of course—and the change in this provision reflects the fact that blood from patients with HH is not harmful to recipients in any way.

The FDA maintains a list of establishments that have received such a variance (http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/RegulationoftheBloodSupply/Variances/ucm164649.htm) As of November 2011, there were more than 100 blood banks on that list.

porphyrias, including PCT, are associated with a blistering, photosensitive rash.[29]

The acute porphyrias—a grouping of several variants, including acute intermittent porphyria and variegate porphyria—typically cause severe abdominal pain and neurologic symptoms, while erythropoietic porphyria patients may present with anemia, hypo- and hyperpigmentation of the skin, red urine, and reddish coloration of the teeth (**FIGURE**).[29] Porphyrias are an often-overlooked cause of neuropathy, as well.[30]

Treatment and follow-up

The abdominal pain associated with porphyria can be treated with dextrose infusions, analgesics, and hematin. Long-term management includes monitoring for cirrhosis, iron overload, and possibly, hepatocellular carcinoma.[27]

The treatment for anemia resulting from ineffective erythropoiesis—which ironically, results in iron overload—is phlebotomy, with 400 mL of blood removed every 2 weeks until the iron overload is relieved.[31] Erythropoietin may be used to treat anemia resulting from phlebotomy, and is thought to mobilize iron stores.[32]

For patients with PCT (and any other porphyria associated with photosensitivity), avoidance of sunlight—and any known precipitating factors—is essential. Hydroxychloroquine 200 mg can be given by mouth twice a week.[33] Fresh blisters should be kept clean and free from infection.

In addition to symptom management, it is important to learn as much as possible about the family history of patients who have, or whom you suspect of having, any variant of this little-known genetic disease. Start with these 2 questions:

1. Do you have family members who are unusually sensitive to the sun?

2. Do you have any family members who always seem to be in the hospital but no one knows what's wrong with them?

Hemochromatosis

Hereditary hemochromatosis (HH), also referred to as iron overload disease, is a little-known genetic disease that primarily affects Caucasians of Northern European descent, although other ethnic groups may also be affected.[34,35]

Iron is such a precious commodity that no mechanism has evolved for excreting it. During times of systemic infection, there is a tendency for the body to "hide" iron from invading bacteria, resulting in an increased serum and tissue ferritin—and causing chronic anemia if this continues for long periods of time. The balance of iron homeostasis depends on the regulation of iron absorption, which HH interferes with. In patients with HH, the excess iron builds up in the body,

A bronze skin tone may be a sign of iron overload associated with hereditary hemochromatosis.

particularly in the liver, heart, pancreas, joints, and pituitary gland, and can cause tissue and organ damage.

Inheritance

Although our understanding of the mechanism by which HH occurs may not be complete, it appears that most cases involve a dysregulation of hepcidin, the major regulator of iron transfer. About 10% of white Americans are carriers of the disorder, which is autosomal recessive, and approximately 0.3% to 0.5% have the double mutation and are therefore at high risk for developing HH.[34,35] In many cases, the disease does not develop until middle age.

Testing

HH often goes undetected for years. In some cases, routine lab tests that reveal a polycythemia with a high serum iron and a high ferritin and elevated liver enzymes are the first indication of a problem.

While iron studies can raise the suspicion of HH, however, pinning down the genetic mutation can be a little more complicated. The most common allele in Caucasians results from a C282Y mutation thought to be traced to a Celtic or Viking who lived several centuries ago. For this reason, patients with signs of iron overload who are of northern European ancestry are sometimes tested immediately for the gene associated with HH. Patients who present with cirrhosis may have had a liver biopsy before HH was suspected, and may be offered genetic testing, as well.[36]

Phlebotomized blood is an excellent source of blood for patients with severe anemia, yet blood banks often discard it.

Clinical presentation

Iron overload results in iron deposits in many tissues, with varying results: Infiltration of the liver can cause cirrhosis, infiltration of the pancreas can lead to diabetes, and infiltration of the skin results in a bronzed appearance. Diabetes is a primary complication when HH—sometimes referred to as "bronze diabetes"—goes untreated.[37]

Treatment

With the exception of a small amount of iron that is sloughed off in dead skin cells each day, bleeding is the only way to rid the body of excess iron. Most patients with HH can be treated with phlebotomy (See "A case for phlebotomized blood)" on page 35. One unit of whole blood is removed at approximately 2-week intervals until the serum ferritin is <20 ng/mL. This process takes about 13 months.[38]

Unlike other genetic disorders, HH can be completely controlled—provided it is detected before major organ damage occurs. Thus, it is particularly important that all family members of an individual diagnosed with HH—or found to be a carrier of the disorder—undergo genetic testing. They should also be asked whether they have (or have had) any relatives who frequently donate blood or have been told to give blood frequently.

A referral for genetic counseling may be indicated, not only for families affected by HH, but for those suspected of having (or carrying) other genetic disorders, as well. JFP

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