Inherited Hematologic and Oncologic Syndromes
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In Brief

Inherited Hematologic and Oncologic Syndromes

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Heritable hematologic disorders are considerably more common than inherited cancer syndromes, ranging from mild conditions marked by laboratory abnormalities to severe and life-threatening diseases. Screening patients who have a positive family history is important to avoid unnecessary interventions, initiate appropriate treatment if necessary, and perhaps most importantly, provide genetic counseling.

Hemoglobinopathies include both the formation of mutated hemoglobin and decreased production of the globin chains. Sickle cell disease is an autosomal recessive disorder caused by a mutation in the β-globin chain. During periods of low oxygen tension, the red blood cells (RBCs) are prone to sickling, leading to vasoocclusion. Some of the consequences of vasoocclusive crisis include bone pain, splenic sequestration, acute chest syndrome, and cerebrovascular accidents. Patients have anemia and increased RBC turnover from hemolysis. The long-term complications of the disease reduce the life expectancy of affected individuals to the mid-40s.

Sickle cell disease is part of the newborn screen in many states. Hemoglobin C and hemoglobin E are less common hemoglobinopathies that lead to mild anemia in the homozygous individual. Compound heterozygotes, S/C or S/E, have more severe disease, with risk for vasoocclusive crises.

Thalassemia does not involve a mutated chain but rather decreased production of a globin chain. Patients who have β-thalassemia trait have decreased production of β-globin chains, leading to a mild microcytic anemia. Different polymorphisms lead to variable production of β-globin. In the most severe form, homozygous patients who have no β-globin production have severe anemia and are transfusion-dependent. Because there are four genes for α-globin production, patients born with α-thalassemia have variable degrees of decreased production of the α-globin chain, depending on how many genes are affected. Loss of all four...
alleles usually leads to fetal demise during pregnancy. For all these diseases, genetic counseling is vital in educating families about potential risks for future children.

Heritable hemolytic diseases include disorders of the RBC membrane as well as disorders of glycolysis. Hereditary spherocytosis, the most common disorder of the RBC membrane, is inherited most often in an autosomal dominant pattern and causes anemia, jaundice, reticulocytosis, gallstones, and splenomegaly. Patients who have a severe phenotype may require splenectomy. As in spherocytosis, the inheritance of hereditary elliptocytosis is autosomal dominant. Many patients are asymptomatic and have mild, compensated hemolysis; patients who have higher percentages of elliptocytes may have mild anemia. All should be screened for gallstones.

Because RBCs lack mitochondria and depend solely on glycolysis to meet their requirement for adenosine triphosphate, deficiencies in the glycolysis pathway lead to chronic hemolysis. Depending on the enzyme deficiency, the hemolysis ranges from mild to severe, with some patients requiring chronic transfusion therapy. Patients also may suffer from hyperhemolytic crises after exposure to infection or drugs. Pyruvate kinase is the most common glycolysis pathway deficiency, but all the enzymes have been implicated, and all are inherited in an autosomal recessive pattern, except for X-linked phosphoglycerate kinase deficiency. As with all patients who are transfusion-dependent, iron overload becomes a major factor in morbidity.

Although enzyme deficiencies of glycolysis are rare, glucose-6-phosphate dehydrogenase (G6PD) deficiency is extremely common, inherited in an X-linked pattern and affecting more than 500 million people worldwide. The major role of G6PD is the production of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), which is critical for preventing oxidative damage to RBCs. Patients born with G6PD deficiency rarely have anemia, except when exposed to oxidative stress, which predisposes the patients to RBC lysis. Although notoriously unpredictable, lysis can occur on a massive scale with exposure to certain medications, infections, or fava beans, leading to profound anemia.

The most common inherited bleeding disorders involving factors of the coagulation cascade are hemophilia A and B, resulting from deficiencies in factors VIII and IX, respectively. The genes for these two factors are located on the X chromosome, and one third of patients have a new mutation and no family history of the disorder. Classically, patients bleed into joints and muscles, but 30% of boys present with bleeding from circumcision. All the other factor deficiencies are much rarer and are inherited in an autosomal recessive pattern. Their bleeding complications range from mucocutaneous bleeding to spontaneous intracranial hemorrhage. von Willebrand disease results from a defect in von Willebrand factor and has several distinct disease manifestations. The most common, type 1, is inherited as an autosomal dominant disorder with variable penetrance. Patients primarily have symptoms of mucocutaneous bleeding: nosebleeds, bruising, heavy menstrual bleeding, and postoperative or postpartum hemorrhage.

Inherited platelet defects include both functional and quantitative disorders. In Glanzmann thrombasthenia, an autosomal recessive disorder, platelets lack glycoprotein Ib/IIa, which binds platelets to fibrinogen, leading to poor clot formation. Patients have normal platelet counts but suffer from recurrent nosebleeds, gastrointestinal bleeding, and menorrhagia. Excessive bleeding from pregnancy, minor surgery, tooth extraction, or trauma can be life-threatening.

Bernard-Soulier syndrome, another autosomal recessive qualitative platelet defect, is caused by a deficiency of glycoprotein Ib, which binds platelets to von Willebrand factor and thrombin. As with Glanzmann thrombasthenia, affected patients have mucocutaneous bleeding, but they may also have thrombocytopenia with characteristic giant platelets.

Among the more common inherited quantitative disorders of platelets is thrombocytopenia with absent radii syndrome, an autosomal recessive disorder characterized by thrombocytopenia and bilateral absence of the radii with presence of the thumbs. In most patients, the platelet count improves slowly, reaching normal concentrations after the first postnatal year. Wiskott-Aldrich syndrome, another quantitative platelet disorder, is X-linked and characterized by small platelets, severely depressed total platelet counts, eczema, and impaired immune function.

Inherited deficiency of any plasma protein that regulates factors in the clotting cascade can predispose to thrombosis. Antithrombin deficiency, inherited in an autosomal dominant pattern with variable penetrance, puts affected patients at risk for venous thrombosis that can occur spontaneously or in relation to pregnancy, oral contraceptive use, surgery, or trauma. Forty percent of patients develop pulmonary embolism. Both heterozygous protein C and protein S deficiency predispose to venous thrombosis and pulmonary embolism, with a more severe phenotype occurring in patients who are homozygous.

The extremely common factor V Leiden mutation results in factor Va being resistant to degradation by activated protein C. The incidence of venous thromboembolism in heterozygote carriers is low but increases in patients who are homozygous for the mutation. Compound heterozygotes for factor V Leiden and deficiencies of antithrombin,
protein C, or protein S are at significantly greater risk of venous thrombosis.

Prothrombin G20210A mutation increases prothrombin biosynthesis by the liver, leading to a predisposition to venous thrombosis. Homozygous deficiency in methylenetetrahydrofolate reductase causes hyperhomocysteinemia and increased risk for arterial and venous thrombosis. Patients who have a family history of pulmonary embolism or recurrent deep venous thrombosis should be screened when placed at particular risk for clot formation, as with prolonged postoperative immobilization or when initiating oral contraceptive use.

Inherited cancer syndromes are rare, but recognizing children who have a family history consistent with a heritable cancer allows for appropriate screening, counseling, and ultimately, decreasing the morbidity and mortality from the predisposition to malignant neoplasms.

Li-Fraumeni syndrome, an autosomal dominant predisposition to cancer caused by a mutation in the \( p53 \) gene, should be considered in a family in which a proband has a sarcoma diagnosed before the age of 45 years, a first-degree relative has any cancer before the age of 45 years, and another first- or second-degree relative has either cancer before the age of 45 years or a sarcoma at any age. Multiple tumors are associated with the Li-Fraumeni phenotype, including soft-tissue sarcoma, osteosarcoma, adrenocortical carcinoma, premenopausal breast cancer, leukemia, and brain tumors. Germline \( p53 \) mutations are reported in 50% to 80% of patients who have adrenocortical carcinoma; fewer than 10% of children who have osteosarcoma or rhabdomyosarcoma; and 1% to 2% of women who have familial, early-onset, or bilateral breast cancer. If patients meet the criteria for Li-Fraumeni syndrome, genetic testing is recommended for mutations in \( p53 \). Screening tests for affected families include renal ultrasonography quarterly and annual total body magnetic resonance imaging.

Patients who have the heritable form of retinoblastoma have a germline mutation in the \( RB1 \) gene. They present at a younger age and have increased propensity for bilateral tumors and multiple primary tumors. Some 15% of patients who have unilateral retinoblastoma carry a germline mutation in \( RB1 \). Because of de novo mutation in the father’s germ cells, 80% of patients who have \( RB1 \) mutations have no family history of retinoblastoma. The probability of being affected is 45% for the offspring of a parent who has bilateral retinoblastoma or for the sibling of a patient who has retinoblastoma if either parent was affected; 7.5% for the child of a parent who has unilateral retinoblastoma; 6% for the sibling of a patient who has bilateral retinoblastoma and unaffected parents; and 1% for the sibling of a patient who has unilateral retinoblastoma with unaffected parents. Patients born with germline mutations in \( RB1 \) are at increased risk for second malignancies, particularly osteosarcoma and melanoma, with exposure to radiation adding to that risk. Screening is guided by the probability of an \( RB1 \) mutation and the family’s preference.

Multiple endocrine neoplasia (MEN) disorders encompass three distinct entities inherited in an autosomal dominant pattern. MEN1, caused by mutations in the gene \( MEN1 \), involves the parathyroid gland, pancreatic island cells, and pituitary gland. Parathyroid involvement is the most common initial manifestation, appearing as early as the second decade. MEN2A affects young children and is associated with medullary thyroid carcinomas, parathyroid adenomas, and pheochromocytomas. In addition to these tumors, patients born with MEN2B present in infancy with skeletal anomalies and ganglioneuromas of the gastrointestinal tract. MEN2A and MEN2B have been linked to the \( RET \) oncogene, which is an activating mutation and does not require loss of the second wild-type allele. Prophylactic thyroidectomy is recommended in all affected children because of the morbidity of medullary thyroid carcinoma.

Familial adenomatous polyposis, also known as adenomatous polyposis coli, is an autosomal dominant predisposition to forming multiple colonic polyps due to mutations in the \( APC \) gene. In addition to the risk of colon cancer, affected carriers are predisposed to upper gastrointestinal tract malignancies, thyroid cancer, medullloblastoma, and hepatoblastoma. Colonoscopy should begin by 10 years of age, and prophylactic colectomy is recommended once extensive polyposis has developed, usually by late adolescence. Surveillance for thyroid cancer is recommended by age 15. Hereditary nonpolyposis colon cancer poses a familial risk of colon cancer, which can present as early as the second decade without the previous development of polyposis. Families are also at risk for uterine, ovarian, and upper gastrointestinal tract cancers.

Patients born with neurofibromatosis (NF) type 1 have mutations in the \( NF1 \) gene, which predisposes them to neurofibromas and optic gliomas as well as malignant peripheral nerve sheath tumors and acute myelogenous leukemia. NF2 involves a mutation in the \( NF2 \) gene, leading to the development of schwannomas, central neurofibromas, and meningiomas.

Several autosomal recessive disorders are associated with an increased risk for cancer. Xeroderma pigmentosum is caused by a defect of DNA repair mechanisms, and affected patients are susceptible to basal and squamous skin cell carcinomas as well as melanomas. Defects in the helicase genes have been described in children born with Bloom syndrome, Werner syndrome, and Rothmund-Thomson syndrome. Patients born with tuberous sclerosis, or tuberous sclerosis complex, have \( tuberous sclerosis complex \) (TSC) mutations in the \( TSC1 \) and \( TSC2 \) genes, which cause hyperplasia of cells of mesenchymal origin, including astrocytes, epithelial cells, and smooth muscle cells, leading to benign tumors of the brain, kidneys, and skin. Tuberous sclerosis is characterized by seizures, intellectual disability, and cutaneous lesions. Papillary renal cell carcinomas are also associated with TSC. Malignant peripheral nerve sheath tumors and acute myelogenous leukemia are also associated with TSC in patients with \( TSC2 \) mutations.
tients who have Bloom syndrome suffer growth impairment and immunodeficiency and are at increased risk of developing many different malignancies, including leukemias, lymphomas, and solid tumors. Children born with Werner syndrome present with premature aging, atherosclerosis, diabetes, cataracts, and increased risk of soft-tissue sarcomas. Rothmund-Thomson syndrome involves a pathognomonic rash called poikiloderma and predisposes to osteosarcoma. In ataxia-telangiectasia, caused by mutations in the ATM gene, patients develop truncal ataxia in early childhood and oculo-cutaneous telangiectasias by age 5. They are immunodeficient and are at increased risk for leukemias, lymphomas, and solid tumors as well as central nervous system tumors. Carriers are at increased risk for breast cancer.

Comment: Another cancer worth mentioning in the context of family risk is Wilms tumor (WT). Although most cases are sporadic, some are associated with genetic syndromes (Beckwith-Wiedemann, WAGR [Wilms tumor, aniridia, genitourinary anomalies, developmental delay], Denys-Drash, congenital aniridia), and approximately 5% are familial. Sporadic and syndromic WT is associated with inactivating mutations of the WT1 gene, a tumor suppressor, on chromosome 11. Familial WT, which follows a pattern of autosomal dominant inheritance with incomplete penetrance, has been associated with mutations on chromosomes 17 (FWT1) and 19 (FWT2).

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In Brief

Growth

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Growth during childhood is tightly regulated and depends on the proper functioning of multiple systems. The process is affected by perinatal factors, including maternal nutrition and uterine size; genetic growth potential inherited from parents; and nutrition throughout childhood. Growth also is affected by the interplay of multiple hormones, including growth hormone (GH), thyroid hormone, insulin, and sex hormones, all of which have varying influence at different stages of growth. Despite all these factors, final adult height generally is restricted throughout the human population to a relatively narrow range: 95% of Americans have a final adult height that falls within only a 6% to 8% variation from the mean. Because final adult height and growth are so well regulated, a deviation from normal expected patterns of growth often can be the first indication of an underlying disorder. Carefully documented growth charts, therefore, can serve as powerful tools for monitoring the overall health and well-being of patients. Key to diagnosing abnormal growth is an understanding of normal growth, which can be classified into four primary areas: fetal, postnatal/infant, childhood, and pubertal.

Fetal growth, influenced by maternal nutrition, uterine size, or restrictions, as well as by insulin and insulin growth factors, actually may have long-lasting effects throughout life. For example, small-for-gestational age and preterm infants have reduced insulin sensitivity later in life that, in turn, has been linked to earlier onset of puberty.

Following birth, growth continues at a rapid rate. Although healthy term...
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