

The inherited bone marrow failure syndromes

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Inherited bone marrow failure syndromes (IBMFS) are rare genetic disorders with defects in the production of red blood cells, white blood cells and platelets leading to varying degrees of aplastic anemia. The syndromes that are primarily single cytopenias include Diamond-Blackfan anemia (DBA), thrombocytopenia absent radii (TAR) and severe congenital neutropenia (SCN). Patients with Fanconi's anemia (FA), dyskeratosis congenita (DC), Shwachman-Diamond syndrome (SDS) and amegakaryocytic thrombocytopenia may develop pancytopenia due to bone marrow aplasia. Common to all these syndromes is a predisposition to malignant change, particularly leukemia; however, solid tumors may develop in FA, DC, and DBA. Most of the patients present during childhood with variable degrees of bone marrow failure. Some of these disorders have characteristic physical abnormalities which facilitate diagnosis. However, physical abnormalities may be absent, and some patients may develop syndrome-specific complications as adults.

Fanconi's anemia (FA) is an autosomal recessive chromosomal instability disorder characterized by multiple congenital anomalies, bone marrow failure and an increased risk of developing leukemia or solid tumors. It is the most frequent of all inherited bone marrow failure syndromes with an overall incidence of approximately 1/360,000 live births and carrier frequency of 1/300.

FA cells are uniquely sensitive to DNA cross-linking agents such as mitomycin C and diepoxybutane (DEB). The standard diagnostic test involves documentation of increased chromosome fragility when dividing cells (usually lymphocytes) are cultured with one of those agents. So far 11 complementation groups (FANCA, B, C, D1, D2, E, F, G, I, J, and L) have been identified and 8 FA genes (FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL and FANCD1 which is BRCA2) have been cloned. About 70% of patients have mutations in FANCA, 10% in FANCC and 10% in FANCG; all other groups are rare. The specific role of

mutations in the FA genes in the pathogenesis of birth defects, bone marrow failure, or oncogenesis is not yet clear.

About 75% of reported cases had birth defects; this may be an overestimate due to under-diagnosis of those with a normal phenotype. The most common presentation is progressive bone marrow failure which develops in approximately 90% of patients. It usually appears early in childhood, at a median age of 7 years. The presence of specific congenital anomalies may be predictive of early onset marrow failure. The life expectancy of an FA patient is about 35 years; the major cause of death is bone marrow failure, followed in frequency by leukemia and solid tumors. Leukemia, almost exclusively acute myeloid leukemia, primarily occurs in teens and young adults. Patients who survive into early adulthood are at a very high risk of developing solid tumors, notably squamous cell carcinoma (SCC) of the head and neck or female genitalia. The reported incidence of solid tumors is 29% by 48 years of age. In approximately 25% of patients with FA who have cancer, the diagnosis of a tumor preceded the diagnosis of FA. Thus there may be underrepresentation of cancers in FA, since FA patients with a "normal" phenotype may never get diagnosed as FA.

We recommend that all patients with characteristic birth defects, aplastic anemia, myelodysplastic syndrome, acute myeloid leukemia and those with early onset characteristic cancers should be tested for FA. Patients suspected of having hematopoietic somatic mosaicism should have a chromosome breakage test on cultured skin fibroblasts.

Hematopoietic stem cell transplantation (SCT) is the only definitive treatment for patients with bone marrow failure. Conventional conditioning regimens have included low-dose cyclophosphamide with thoracoabdominal irradiation. Long term survival following HLA-compatible sibling donors may be as high as 80%. The outcome following unrelated donor transplants is lower (around 33%). Transplant is associated with an increased risk and earlier onset of

head and neck SCC. Recent promising transplant modalities are using Fludarabine-based preparative regimens to increase immunosuppression, graft manipulation to reduce GvHD, and better HLA matching; long-term outcome is awaited.

Patients with bone marrow failure who have matched sibling donors should be offered SCT. Patients who lack a sibling donor may be treated with androgens; an initial response may be seen in approximately 60%. Patients refractory to medical therapy or those with leukemia or MDS should consider proceeding directly with an alternate donor stem cell transplant.

All FA patients should undergo risk-based, age-appropriate surveillance at regular intervals by all of the necessary subspecialties. Pediatric patients are at an increased risk of adverse hematologic outcome, and adults are at risk of solid tumors. SCT patients are also at risk of early head and neck SCC. Patients on androgens have an increased risk of hepatic tumors. Females need to have annual surveillance for gynecological malignancies. Once a tumor develops, management should include maximization of surgical intervention while keeping chemotherapy and radiotherapy use to a minimum.

DBA is a heterogeneous disorder with regard to pattern of inheritance, associated anomalies, age at presentation, clinical course and response to therapy. Most of the patients present in infancy with severe anemia, reticulocytopenia and decreased or absent erythroid precursors in the bone marrow. Red cell adenosine deaminase is elevated in about 70-90% of patients and may be used to distinguish DBA from other pure red cell aplasias and to identify silent carriers within a family. A definitive diagnosis is now possible in about 25% of the patients who have a mutation in the RPS19 gene. There are at least two other genes awaiting identification. Approximately 60% of the patients initially respond to steroid treatment. Those that are unresponsive or develop resistance must be maintained on chronic transfusions. Allogeneic stem cell transplantation (SCT) may be curative. Patients with DBA are not only at increased risk for developing leukemias, but also solid tumors, in particular osteogenic sarcoma.

DC is characterized by a triad of cutaneous reticulate hyperpigmentation, nail dystrophy and mucosal leukoplakia. It is associated with mutations in some of the genes involved in the telomere maintenance pathway. The X-linked form is generally more severe; there are mutations in DKC1. Some patients with the autosomal dominant (AD) form are heterozygous for mutations in TERC, the RNA component of telomerase. There may be other genes for AD DC.

The genes for the recessive form remain unidentified at this time. Premature mortality is primarily caused by bone marrow failure, solid tumors, or pulmonary fibrosis. Anabolic steroids may improve the hematopoietic function for a variable period of time. Allogeneic SCT has limited success in DC.

SDS is an AR disorder characterized by exocrine pancreatic insufficiency, neutropenia, and metaphyseal dysostosis. Patients usually present in infancy. The main complications include bone marrow failure, myelodysplastic syndrome, and leukemia. Mutations in the SBDS gene are present in the majority of patients. G-CSF and androgens form the mainstay of treatment for the hematological manifestations. Allogeneic SCT may be curative for those with refractory bone marrow failure or leukemia.

TAR is an AR disease characterized by hypomegakaryocytic thrombocytopenia and bilateral absent radii with the presence of thumbs. Thrombocytopenia is often profound at birth, but usually improves during the first few years of life. Mortality in early infancy can be reduced by vigorous platelet support. Four patients have been reported with leukemia.

SCN is an AD disorder with severe neutropenia and pyogenic infections in early infancy. The majority have heterozygous mutations in the gene encoding neutrophil elastase (ELA-2); a few had mutations in GFI-1. Early mortality was very high before the era of G-CSF. More than 90% of the patients show sustained response to G-CSF. About 10% of the patients have developed leukemia. Hematopoietic SCT is the treatment of choice for patients refractory to G-CSF.

Congenital amegakaryocytic thrombocytopenia is characterized by severe thrombocytopenia due to a lack of megakaryocytes in the bone marrow. The disease is caused by mutations in the c-mpl gene coding for the thrombopoietin receptor. Most patients with this disorder go on to develop aplastic anemia; leukemic transformations have been reported. SCT has been shown to be the only curative treatment for patients with amegakaryocytic thrombocytopenia.

IBMFS are cancer susceptibility syndromes. IBMFS gene products may be involved in cancer pathways, and thus the IBMFS may serve as models for understanding the pathophysiology of specific malignancies. Patients with these disorders need life-long surveillance for the development of cancer. SCT may cure the hematologic manifestations, but the overall risk of cancer remains high. Standard SCT conditioning regimens may be too toxic for patients with some of these disorders and may need to be tailored to individual diseases.

Suggested Reading

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