Fanconi Anemia

Fanconi anemia is the most common inherited cause of aplastic anemia. It is due to an autosomal recessive defect in a gene coding for proteins involved in DNA interstand crosslinking repair mechanisms. Clinical features of Fanconi anemia include short status, microcephaly, thumb and forearm malformations, Cafe-au-Lait spots, ocular abnormalities, and renal anomalies (such as horshoe kidney). Diagnosis begins with lab tests and chromosomal analysis. Often, macrocytic anemia and pancytopenia are evident. The management for Fanconi anemia involves monitoring for malignancy and bone marrow failure as well as consultation with a transplant team for hematopoietic stem cell transplantation (HSCT).



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Characteristics

Autosomal Recessive
Recessive-chocolate
Various genes have been associated with Fanconi anemia including BRCA2. These genes code for proteins that play an important role in DNA crosslinking repair and genomic stability. The most common inheritance pattern in Fanconi anemia is autosomal recessive. Fanconi anemia due to FANCB mutations are X-linked.

Aplastic Anemia
A-plastic-bottle Anemone
Aplastic anemia is a life-threatening condition that occurs when there is failure of blood cell production leading to pancytopenia. Fanconi anemia is a hereditary cause of aplastic anemia.

DNA Crosslink Repair Defect
Defective DNA Repair-man Falling and Broken DNA
The main defect in Fanconi anemia is the inability of cells to repair a type of DNA damage that consists in interstrand crosslinks which leads to genomic instability. The resultant genomic instability makes cells vulnerable to cytotoxic agents and predisposes patients to the development of malignancies. The DNA crosslink repair defect and the genomic instability also results in loss of hematopoietic stem cells which can result in bone marrow failure.

Clinical Presentation

Short Stature
Shorts Statue
40-60% of patients with Fanconi anemia present with short stature. Short stature is defined as height that is 2 standard deviations or more below the mean for age and sex.

Microcephaly
Small-head
Microcephaly corresponds to an abnormally small head and is defined as a head circumference that is over 2 standard deviations below the mean for age and sex or below the 3rd percentile. Other abnormalities include triangular facies and webbed neck.

Thumb and Forearm Malformations
Abnormal and Duplicated Thumb and Absent Radial Bone
Over half of the patients with Fanconi anemia present with thumb or forearm abnormalities. Patients may present with an absent thumb, hypoplastic thumb, bifid/duplicated or triphalangeal thumbs. Among the forearm abnormalities, patients may present with absent or hypoplastic radii bones.

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Cafe Au Lait Spots

Coffee-cow

Café-au-lait spot is the term given to hyperpigmented macules and patches that range from light brown to dark brown. These lesions are present in various underlying conditions such as neurofibromatosis type I. Patients with Fanconi anemia usually presents skin findings including café-au-lait spots.

Ocular Abnormalities

Crazy Eyes

Approximately 20 to 40% of patients with Fanconi anemia present with eye abnormalities including strabismus, microphthalmia and hypo-, and hypertelorism. Patients with Fanconi anemia need to be evaluated by an ophthalmologist to detect ocular impairments and provide early management.

Horseshoe Kidney

Horseshoe Kidneys

Horseshoe kidney is a congenital renal disorder characterized by the fusion of both kidneys giving it a horseshoe shape. Approximately 20 to 30% of patients with Fanconi anemia present with renal and urinary tract malformations such as horseshoe kidney.

Lab Findings

Chromosomal Breakage Testing

DNA with Breaks and Test-tubes

Initial screening involves peripheral blood smear to evaluate for chromosomal breakage in T-lymphocytes when exposed to cytotoxic agents such as mitomycin C or diepoxybutane (DEB). If the test is negative but there is high suspicion, the chromosomal breakage studies are repeated on skin fibroblasts. If the test is positive, it is confirmed with Fanconi anemia gene sequencing.

Macrocytic Anemia

Macaroni Anemone

Macrocytic anemia is when the median corpuscular volume (MCV) is >100 fL. Fanconi anemia is usually macrocytic, although it can be normocytic (80-100 fL).

Pancytopenia

Pan-side-toe-peanut

Pancytopenia refers to a reduced number in all blood cell lines. Fanconi anemia can lead to bone marrow failure which is when there is a deficiency in the hematopoietic stem cells resulting in insufficient blood cell line production and consequent pancytopenia. Mild to moderate cytopenias are present in over 70% of patients at the moment of diagnosis. Progression to pancytopenia is variable and can occur rapidly after initial diagnosis or may take years to develop.

Management

Monitor For Malignancy and Bone Marrow Failure

Monitor and Bone Marylin-Monroe Suppressed by Malignant Man

Since the genes involved in Fanconi anemia code for proteins that play an important role in DNA crosslinking repair mechanisms, patients with this condition are at increased risk of DNA replication impairment, mutations and chromosomal aberrations. They are at high risk for developing bone marrow failure. Therefore, follow-up labs and annual bone marrow biopsy are usually recommended. Furthermore, due to the increased risk for leukemia and solid tumors especially in the head and neck region, monitoring for malignancy according to guidelines should also be performed.

Hematopoietic Stem Cell Transplantation

Stems with Blood Cells in Transplant Train-plant

When patients present with moderate to severe cytopenia or with high risk cytogenetic results such as clonal abnormalities, an allogenic hematopoietic stem cell transplantation (HSCT) may be indicated. Patients with bone marrow failure but no HSCT donors are sometimes treated with androgens such as danazol to stimulate erythropoiesis.

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