Identification of Congenital Marrow Failure Syndromes in Children and Adults

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Objectives

1) Identify the most common inherited bone marrow failure syndromes and children and adults

2) Discuss common presenting symptoms and diagnostic criteria for the most common inherited bone marrow failure syndromes in children and adults
Inherited Bone Marrow Failure Syndromes (IBMFS)

- Important to identify because this will influence:
  - Transplant management (donor, preparative regimen, etc…)
  - Risks of complications
  - Genetic and medical counseling and family surveillance
- Potentially informs the diagnosis of “acquired” aplastic anemia

Fanconi Anemia

- First described in 1927, since then >2000 cases described
- Started diagnosing based on birth defects and aplastic anemia then moved to diagnosing based on response to DNA-crosslinking agents (such as Diepoxybutane or Miromycin C). Now will also use gene sequencing.
- Typically macrocytic anemia with elevated fetal hemoglobin
- High risk for bone marrow failure, acute leukemia and solid tumors

Shimamura, Blood Reviews 2010 24: 101-122
Molecular pathology

- FA genes interact with BRCA and others to repair DNA interstrand crosslinks
- 21 FA genes have been identified (FANCA most common, making up 60-70%)

Physical features

- In the literature, ~60% showed some physical abnormality* including:
  - Integumentary- Café au lait spots, hyper/hypopigmentation
  - Skeletal:
    - Short stature
    - Upper limbs- Thumbs (absent/hypoplastic, etc…), radii, hands (clino/polydactyly)
    - Head- Microcephaly, hydrocephaly
  - Eyes- small, hyper/hypotelorism*
  - Other (horseshoe kidney, hypospadias, DD, deafness, syndactyly of feet, club feet, GI tract atresia, absent corpus callesum)

*Shimamura, Blood Reviews 2010 24: 101-122
However…. 

- While there may be a majority with physical findings, there is a clear cohort who are discovered to have FA based on testing done when a relative is discovered to have it or they develop AA or a malignancy later on in life.

- Rosenberg et al, found that those with more congenital abnormalities were at higher risk for early onset bone marrow failure, while those without many of these abnormalities were at higher risk for leukemia and solid tumors as young adults.


Cancer predisposition risk

- Median age for surviving free from cancer is 29yo

- AML most frequent malignancy (other leukemias rare)

- Head and neck Squamous Cell Carcinoma most common solid tumor (also esophageal, vulva/anus and brain)

- Relative risk of these cancers in the FA population is hundreds to thousand times greater than the general population

Shimamura, Blood Reviews 2010 24: 101-122
FA in the Adult population

- 3 main groups to discuss:
  - Those with known FA who have NOT been transplanted
  - Those with known FA who are transplant survivors
  - New diagnoses in adulthood

FA who have NOT been transplanted

- May yet develop bone marrow failure and need transplant
- May need chelation for iron overload
- Need aggressive surveillance by ENT and Gynecology for solid tumors as well as surveillance for hematologic malignancies
Transplant Survivors

- Monitor for GVH and hematologic relapse
- Monitor for solid tumors as above, one study suggests that these occur at a younger age than those who haven’t been transplanted
- Those with cGVH of the oral mucosa are at especially high risk of head and neck malignancy


New Diagnoses

- At least 10% of all FA diagnoses are ≥16 yrs old
- Diagnosis when screened due to proband family member diagnosed, or more likely when a clinically atypical solid tumor is diagnosed
- One study found that in FA patients who developed solid tumors 20% discovered that they had FA after the diagnosis of their solid tumor
- Often have minor or no phenotypic abnormalities and normal blood counts

When to screen for FA?

- Adult patients should be screened for FA if they have any of the following conditions:
  - Aplastic anemia (AA) or severe cytopenias not responding to standard therapy
  - Myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) associated with unusual cytogenetic results such as 1q+ or 3q+
  - Solid tumors that develop at a younger than expected age, in patients without known risk factors
  - Severely delayed blood count recovery or aplasia after chemotherapy
  - Unusual sensitivity to radiation therapy
  - Decreased fertility or early menopause

Dyskeratosis Congenita

- Originally Zinsser-Cole-Engman syndrome after the physicians who first described it in the 1930's
- In the 60's the dermatologic phenotype was associated with the hematologic problems
- Male predominance (3.2:1 M:F)*
Physical features

- 75% had some part of the classic triad of dystrophic nails, lacy reticular pigmentation and oral leukoplakia (70%, 67%, 47% respectively). 46% had all 3
- Can also see lacrimal duct stenosis, DD, poor dentition and early gray hair
- Esophageal stenosis in 8%
- 2 severe subsets:
  - Hoyeraal-Hreidarsson (HH) with cerebellar hypoplasia, IUGR, microcephaly and early SAA
  - Revesz Syndrome (RS) with bilateral exudative retinopathy, IUGR and CNS calcifications

Shimamura, Blood Reviews 2010 24: 101-122

Clinical features of DC. The clinical features of DC are: nail dystrophy (A), oral leucoplakia (B), abnormal skin pigmentation (C), cerebellar hypoplasia (D; highlighted by the arrow), and premature hair loss/greying (E).

Inderjeet Dokal Hematology 2011;2011:480-486

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Other findings

- Risk of SAA 50% by age 50
- Often found when poor response to SAA treatment
- Diagnosed based on telomere length in several leukocyte subsets (and can sequence DC genes*)
- Familial pulmonary fibrosis can be a presenting complaint
- Typically MDS, AML or aplastic anemia (most common solid tumor is HNSCC)
- Median age for CA free survival is 68 yo

Diamond-Blackfan Anemia

- 98% diagnosed in the first year of life (hence it just gets 1 slide)
- Diagnosis clinical based on macrocytic anemia with reticulocytopenia under 12 months, increased erythrocyte ADA and elevated HgbF. Genes described but not required for Dx.
- 25% have physical abnormalities, most common short stature and thumb abnormalities (also cleft palate, eye abnormalities)
- If Diagnosed in older patients is due to late recognition of chronic anemia, anemia during pregnancy or found in silent carriers when a family member is diagnosed
- Low risk for malignancy and SAA
- Known mutations causing DBA encode protein components of ribosomal subunits
- Responds well to steroids and pRBC transfusions

Vlachos, Br J Haematol 2008; 142 (6): 859-876
Shwachman-Diamond Syndrome

- Originally found as a combination of exocrine pancreatic insufficiency and neutropenia
- Aplastic Anemia in about 20% by age 3 yo
- Can see evolution to AML or MDS, median age of 37 years for developing cancer
- Physical characteristics are:
  - Short stature
  - Metaphyseal dysostosis
  - Abnormal Thorax (Jeune sm, pectus carinatum)

SDS diagnosis

- Pancreatic enzymes (trypsinogen and pancreatic isoamylase) in combination with neutropenia and BM findings (hypocellularity, often decrease of myeloid precursors). Anemia in up to 80% also
- Genetic diagnosis (confirmation) by testing for a known SBDS gene mutation
### Other IBMFS

- Severe Congenital Neutropenia
- Amegakaryocytic Thrombocytopenia
- Thrombocytopenia absent Radii
- Radioulnar synostosis
- Pearson syndrome