Hematologic and Oncologic Conditions in Down Syndrome: An Overview for the Primary Care Provider

Heme/onc conditions in Down syndrome (DS) are rare, seen in only 1 to 2 percent of individuals with DS. However, the consequences can be serious. This document will review the spectrum of associated heme/onc conditions as well as important screening guidelines.

**WHAT ARE THE MOST COMMON HEME/ONC ASSOCIATIONS WITH DOWN SYNDROME?**

**Transient Myeloproliferative Disorder (TMD)**
- TMD develops in about 1 in 10 infants with DS and is seen almost exclusively in newborns with DS. TMD is a disorder of at least one hematopoietic cell line thought to stem from an abnormality of fetal liver blood cell production.
- A clonal population of blasts is found, often along with anemia and/or thrombocytopenia.
- Management is typically supportive with transfusions as needed.
- Leukopheresis is recommended if WBC>200k. Provision of cytotoxic therapy is controversial and highly individualized.
- Brief treatment with low dose cytotoxic therapy is occasionally required.
- While TMD is most often benign with spontaneous resolution by 3 months of age, affected neonates may develop life-threatening complications including hydrops, hepatosplenomegaly, and cutaneous or organ infiltrates.
- Additionally, 10 to 30 percent of children with TMD will develop leukemia (most often acute megakaryoblastic leukemia (AMKL) later in life. This is a type of AML. Thus, TMD is considered a pre-leukemic disorder, requiring close hematology follow-up (CBC with diff every 3 months until 3 years of age, and then every 6 months until 6 years of age).

**Polycythemia**
- About 65 percent of infants with trisomy 21 have polycythemia (venous hematocrit >65%) in the first few months of life.
- This occurs even in children without cyanotic heart defects and is thought to be secondary to increased erythropoietin levels in the setting of chronic fetal hypoxemia.
- Polycythemia typically resolves on its own; partial exchange transfusion is controversial but may be indicated if hematocrit is >70%.

**Iron-deficiency anemia**
- A hemoglobin level should be obtained annually from 1 to 21 years of age to screen for anemia.
- Iron-deficiency is the most common etiology of anemia in children with DS (as well as worldwide). This is due to decreased dietary intake of iron because of hypotonia, dysphagia and delayed oral motor skills.
Acute leukemia

- Children and adults with DS are 10 to 20 times more likely to develop acute leukemia. However, because leukemia is quite rare in general, only 1 to 1.5 percent of individuals with DS will develop leukemia. Lymphoblastic and myeloblastic forms occur equally.

- Acute myeloid leukemia tends to occur between ages 1 and 5. The AKML subtype is the most common among children with DS. The gene GATA1 located on chromosome 21 encodes for a hematopoietic growth factor. GATA1 has been shown to be involved in the pathogenesis of both TMD and AKML in children with DS as well as in leukemic blasts of patients without DS. Children with DS-related AML have lower rates of relapse and improved sensitivity to standard chemotherapy compared with those without DS.

- Acute lymphoid leukemia (ALL) is typically seen between ages 3 to 6 in children with DS. The presentation of ALL in DS is similar to non-DS ALL. However, children with DS-related ALL tend to be more sensitive and susceptible to toxicity from therapy with methotrexate (difference in metabolism is thought to be linked to enzymes encoded for on chromosome 21). Unlike those with AML, children with DS who develop ALL have a worse prognosis than those without DS.

Germ cell tumors

- Individuals with DS have a 5 to 50 times increased incidence of testicular cancer, especially germ cell tumors. While cryptorchidism has been implicated as a risk factor, the etiology for the increased risk is not completely understood.

WHAT CANCERS ARE INDIVIDUALS WITH DOWN SYNDROME LESS LIKELY TO GET?

Individuals with DS tend to have a lower incidence of most solid tumors, specifically: CNS and peripheral nerve tumors, neuroblastomas and Wilms tumors, along with bronchial, nasopharyngeal, urinary tract, uterine, breast and skin carcinomas.

HOW RELIABLE ARE THE TYPICAL HEMATOLOGICAL INDICES IN DOWN SYNDROME?

- The erythrocyte MCV in children with DS tends to be elevated. The exact pathophysiology and etiology are unknown, but they are thought to be related to the direct presence of an extra chromosome 21 rather than to some surrogate such as heart disease or hematocrit. This makes the MCV a poor indicator in the diagnosis of iron deficiency anemia in children with DS.

- The white blood cell count is often low in DS. A low platelet count is rare and should be cause for concern.

HOW OFTEN SHOULD YOU CHECK A CBC AND/OR HEMOGLOBIN?

The AAP guidelines recommend screening newborns with DS with a CBC and differential to evaluate for myeloproliferative disorders, polycythemia, anemia, and thrombocytopenia. The AAP guidelines then suggest annual screening of hemoglobin. If there is a concern for a diet low in iron or if hemoglobin is <11, it is recommended to order a ferritin or CRP or reticulocyte hemoglobin, as the MCV can be an unreliable predictor. If CRP is elevated, then the ferritin is not reliable as both can be acute phase reactants.

WHAT SIGNS AND SYMPTOMS SHOULD I TELL PARENTS TO LOOK OUT FOR?

- Excess fatigue
- Lethargy
- Major change in feeding pattern
- Shortness of breath
- Easy bruising
- Petechiae

- Pain in legs
- Limping