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APPROACH TO SICKLE CELL DISEASE

Background

Definitions

- Worldwide, sickle cell disease is caused by one of the most common autosomal recessive gene defects.
- The wild type adult beta-chain hemoglobin is denoted as HbA. The Sickle cell mutant beta-chain is denoted as HbS.
- The specific Sickle cell mutation is an Adenosine to Guanine substitution resulting in a substitution of hydrophobic valine for glutamic acid at position 6 of the beta-chain, reducing its solubility under deoxygenated conditions.
- Sickle cell anemia describes homozygosity for hemoglobin S (HbSS) while sickle cell disease describe all the conditions resulting from the phenomenon of sickling.

Background Physiology

- Sickle cell disease occurs when an affected individual inherits HbS from both parents and has the resultant genotype of HbSS. It can also result when HbS from one parent is combined with another beta chain abnormality from the other parent, such as beta thalassemia or HbC.
- Heterozygous individuals have more than 50% normal hemoglobin and are typically asymptomatic.
- The Sickle cell mutation confers abnormal properties to the red blood cell. When deoxygenated, the mutant hemoglobin polymerizes and distorts the RBC into a crescent or sickle shape with reduced deformability. Adherence of the RBCs to the vascular endothelium results in the slowing of blood flow, vaso-occlusion of small vasculature and intimal hyperplasia. Consequently, individuals are predisposed to ischemic damage to organs, painful crises, splenic dysfunction, growth retardation, hemolytic anemia and an increased vulnerability to infection (see table of clinical manifestations).
- With newborn screening offered for Sickle Cell Disease in most provinces in Canada, the diagnosis is usually made at birth, prior to the presence of symptoms. The first presentation of symptoms is usually with dactylitis (acute pain in hands and/or feet) and can occur, at any time during childhood (60 % by 2 years of life, 96% by 8 years of life).
- Overall survival of patients with Sickle Cell Disease is reduced but with advances in medical care survival is improving. Successful interventions include treatment with hydroxyurea (increases HbF production), antibiotics (considering functional asplenism) and more rapid care in cases of disease complications.

- Bone marrow transplant is the only curative treatment available.

The majority of treatments are aimed at reducing the frequency of painful crises and reducing their severity.

Questions to ask

a) Family History
Sickle cell is the most common single gene mutation afflicting individuals of African descent [1/375]. It is also common in those of Mediterranean, Turkish, Arabian and Indian descent.

b) Anemia
Excessive tiredness, fatigue, SOB, pallor

c) Pain crises
Acute painful episodes are the most common presentation of Sickle cell.
Persistent pain in bones, chest or abdomen

d) Signs of hypovolemia
Poor urine output, lack of tears, thirst

e) Acute chest syndrome
Cough, dyspnea, chest pain

f) Hand/ foot syndrome
Swollen and painful hands or feet

g) Stoke
Affects 10% of Sickle cell patients: sudden neurological deficits

h) Infection
Malaise, cough, chest pain, diarrhea, vomiting

i) Vaccinations
Children with Sickle cell are particularly prone to infection and should be immunized with the standard childhood regime plus 23-valent pneumococcus vaccine and an annual influenza vaccine. Meningococcal vaccine should be considered in adolescence.

j) Previous medical history
All patients with Sickle cell should be followed by a specialist clinic. Therefore, these clinics should be used as an excellent source of information on disease severity, past manifestations and treatment regimens.

k) Diet
Adequate iron and folic acid due to high RBC turnover

Make sure to have patients avoid
Dehydration, overexertion and exposure to cold which increases the risk for vaso-occlusive crises.

Physical Examination

At every visit one should examine the following

- **Vitals**
  Oxygen saturation, heart rate, respiratory rate, blood pressure and temperature
- **Growth parameters**
  Growth delay and delay of sexual maturation is common
- **General Appearance**
  Severe distress – Patients are at risk for serious presentations such as MI or stroke, chest crisis, bacteremia and sepsis which will require immediate intervention.
  Abdominal exam
  Splenomegaly may be appreciated initially, after which the spleen size regresses
- **Skin**
  - Cyanosis
  - Pallor of skin, lips or nail bed
  - Ulcers
  - Jaundice
- **Respiratory**
  Signs of infection or edema
- **Ophthalmology**
  Acuity
  Detailed retinal exam: neovascularization, detachment and “black sunburst” hemorrhages
- **MSK**
  Inability to move extremities
  Painful swelling of hand and/or feet

Investigations

Laboratory investigations

- **Blood analysis**: CBC. Chronic hemolysis associated with a mild anemia with reticulocytosis. That said, patients are at risk for acute severe anemia when the bone marrow supply does not meet demands, such as with an aplastic crisis (eg. parvovirus B19 infection) or with a splenic sequestration crisis.
- **Hemolysis studies**: May see unconjugated hyperbilirubinemia, increased LDH, low haptoblobin.
- **Peripheral smear:** reveals sickled red cells, polychromasia (reticulocytes), Howell Jolly bodies (signifies asplenism)
- **Hemoglobin studies**: hemoglobin electrophoresis – HbF usually elevated
- **End organ damage**: Kidney and Liver function
- **Bacterial cultures:** if fever present

- **Urinanalysis**: as part of septic workup, also to investigate kidney function, and the ability of kidney to concentrate urine

Imaging Studies

- Plain X-rays
- Transcranial Doppler ultrasound or MRI to assess risk for/ diagnosis of stroke
- Bone scan to differentiate bone pain from pain crises from that of osteomyelitis

Table: Major clinical manifestations in SCD

General	Acute Pain Crisis	There is considerable variability in the intensity and frequency of acute pain episodes. From less than one to six episodes requiring hospitalization per year in one study.
CNS	Stroke	25% of children with sickle cell anemia have silent ischemic lesions that may impair neurocognitive function.
	Epilepsy	Epilepsy is 3 times more common in SCD patients than the general population.
Endo	Growth failure	Multifactorial.
	Delayed sexual maturation	Pathogenesis is uncertain, although primary hypogonadism, hypopituitarism and hypothalamic insufficiency are possible contributors.
ID	Asplenism	By 1 year of age most children are hyposplenic, by 4 years asplenic, putting them at risk for bacteremia, meningitis, osteomyelitis, etc. Most common organisms: Strep Pneumonia (#1), H Influenza b (#2). Penicillin is used prophylactically.
Cardio	MI	Due to vaso-occlusive crisis, at risk for CVA.
	Cardiomegaly	Increased cardiac output in face of chronic anemia leads to LVH. With pulmonary hypertension, develop RVH. May also develop CHF.
MSK	Osteoporosis	Due to increased hematopoiesis (marrow spaces extend causing tower skull, frontal bossing, thinned trabeculae) and/ or bone infarction.
	Acute pain crisis	Bone infarction and necrosis results in excruciating pain
	Osteomyelitis	Strep Pneumonia most commonly.
Hepatic	Cholestasis	Benign

	Iron overload	Due to frequent transfusions
	Cholelithiasis	Secondary to pigmented gallstones (increased bilirubin)
GU	Priapism	Emergency
Pulmonary	Acute Chest syndrome	Pneumonia leads to V:Q mismatch, increases O2 tension and increases thrombosis due to sickling. Embolic fat emboli (from bone marrow infarction) can also be instigating event. Up to 50% of patients will have an acute chest crisis. This is the leading cause of death. Long term complications include pulmonary hypertension and chronic lung disease.
Renal	Renal failure	Due to chronic occlusion of renal vasculature. Up to 18% of patients will develop renal failure.
	Enuresis	Due to a) loss of urea gradient and concentrating ability of kidney medulla or b) nephrogenic Diabetes Insipidus.
	Hematuria	Papillary infarcts
Retina	Retinopathy	Retinal vessel proliferation due to retinal artery occlusion, retinal detachment and hemorrhage may result.

Differential diagnosis

- Rheumatic fever
- Septic arthritis
- Osteomyelitis
- Trauma
- Congenital syphilis
- Acute abdominal disorders
- Various severely painful medical conditions
- Drug seeking behavior

References

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