13. GROWTH AND ENDOCRINE COMPLICATIONS

Principles

- To maintain a system for close monitoring of growth and development.
- To prevent transfusion-related endocrine complications.
- To enable early detection of endocrine disorders with timely and appropriate intervention.

Recommendations

Monitoring

- The growth, nutritional status, and development for children with SCD should be monitored every 6 to 12 months during routine, follow-up, pediatric-clinic visits, and plotted on an appropriate growth chart until patients have attained adult height and full sexual development.
- Each specialist centre should collaborate with a pediatric or an adult endocrinologist who has knowledge of endocrine complications in SCD.
- Children should be referred to a pediatric endocrinologist if there is a clinical suspicion of growth failure or any endocrine-related complication.
- Adolescents and adults with SCD should be routinely monitored for endocrine disorders including diabetes mellitus, hypothyroidism, hypoparathyroidism, hypogonadotrophic hypogonadism, and growth-hormone deficiency. Any abnormalities should prompt a consultation with an endocrinologist.

Delayed Growth and Growth Failure

- Height and weight monitoring should be performed at each visit (and at least every 6 to 12 months) for all children with SCD, and plotted on an appropriate growth chart.
- Nutrition counseling should be provided during routine clinic visits.
- Folic-acid supplementation is recommended due to increased folate utilization and red blood cell turnover.
- Patients should be tested for zinc deficiency. Zinc supplementation has been shown to improve growth and gonadal function and decrease infection rate among children with SCD.\(^5,1,5,16\)
- Children with heights <5\textsuperscript{th} percentile for age, despite adequate nutritional status, should be referred to a pediatric endocrinologist for growth-hormone stimulation testing and, if indicated, growth-hormone therapy.
- Patients with poor growth associated with severe anemia should be strongly considered for hydroxyurea therapy, unless they are already on a chronic transfusion program.
- The diagnosis of growth-hormone deficiency, other hormonal or nutritional deficiencies, or deferoxamine toxicity should be considered for children with short stature or growth failure.

Hypogonadism and Delayed Puberty

- Children and adolescents with SCD who lack any pubertal signs by the age of 13 years in girls and 14 years in boys should be referred to a pediatric endocrinologist for evaluation.
- All patients with delayed puberty or hypogonadism should undergo investigations for bone age and hormonal assessments, as well as referral to an endocrinologist for further management.
- Adults with sickle cell disease should be routinely evaluated for secondary hypogonadism, impotence, or infertility.

Adrenal dysfunction

- Children and adults with SCD are at risk of pituitary-adrenal axis dysfunction secondary to hemorrhagic or thromboembolic injury and iron deposition.
- Clinicians should have a low threshold to investigate for adrenal insufficiency among patients who have hemodynamic compromise during sickle cell crises or with sepsis.
**Thyroid Dysfunction**
- There are conflicting data regarding the significance of thyroid dysfunction among children and adults with sickle cell disease.
- Chronically transfused children and adults with SCD are at increased risk of hemosiderin-associated thyroid dysfunction and should undergo annual thyroid screening.
- Children and adults with evidence of hypothyroidism should receive thyroid-hormone replacement therapy, and should be referred to an endocrinologist.

**Impaired Glucose Tolerance and Diabetes Mellitus**
- Diabetes mellitus (DM) affects approximately 2% of chronically transfused patients with SCD. \(^\text{13}\) Duration of chronic transfusions and age at the initiation of chronic transfusion therapy are the most important risk factors for these patients. \(^\text{13}\)
- Hemoglobin A1c may not be a reliable indicator of hyperglycemia in patients with SCD. \(^\text{17,18}\)
- Chronically transfused children and adults with SCD should undergo annual glucose tolerance screening with fasting plasma glucose from 10 years of age.
- Impaired glucose tolerance and diabetes should be managed as per the Canadian Diabetes Association Guidelines, \(^\text{19}\) and in conjunction with a diabetes clinic, with emphasis on glycemic control, diet, exercise, and management of complications.

**Parathyroid Dysfunction**
- Hyperparathyroidism is rare, but may occur as an incidental finding (no known association with SCD). Symptoms are non-specific, but, more importantly, may mimic other complications of SCD, such as bone pain, polyuria, and fatigue. \(^\text{20}\)
- In patients with severe and recurrent bone pain, consider screening with serum calcium, phosphorus, alkaline phosphatase, renal function, parathyroid hormone levels, and neck ultrasound to exclude hyperparathyroidism.
- Hypoparathyroidism may occur from iron overload as seen in transfusion-dependent beta thalassemia patients. \(^\text{21}\) Consider screening chronically transfused patients from 10 years of age.
- Children and adults with evidence of hyperparathyroidism should be referred to an endocrinologist.

**Background**
Delayed growth, skeletal maturation, and pubertal development are the most common endocrine disorders among children with sickle cell disease (SCD). Children with SCD often maintain a lower average height and weight than children without SCD. \(^\text{2}\) A widely accepted definition of pubertal delay is the absence of pubertal signs by 14 years of age for boys and 13 years of age for girls. \(^\text{3}\) Children and adolescents with SCD are frequently affected by delays in sexual maturation and late pubertal onset. \(^\text{4,5}\)

These growth abnormalities are seen more commonly among children and adolescents with homozygous hemoglobin SS disease than among those with SCD. \(^\text{6}\) There are several factors that contribute to growth delay and failure among children with SCD. \(^\text{1,7,8,9,10}\) Infants and young children are particularly at risk for suboptimal nutritional intake during/following an acute illness. \(^\text{11}\) Careful counseling and close follow-up are necessary to monitor for and prevent these common complications.

Other endocrine disorders that may occur include adrenal, thyroid, pancreatic, and parathyroid dysfunction. Although these disorders can manifest among non-transfused patients with SCD, these complications tend to be more common among chronically transfused children and adolescents with SCD as a consequence of iron overload. \(^\text{12-14}\) For children and adults with SCD, the etiologies for these endocrine abnormalities are multifactorial, and these disorders may arise as a consequence of chronic anemia, tissue hypoxia, high basal energy demands, iron overload, genetic factors, and malnutrition. \(^\text{13}\)
References


