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.[5,15,16]
- Children with heights <5th 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.[13] Duration of chronic transfusions and age at the initiation of chronic transfusion therapy are the most important risk factors for these patients.[13]
- Hemoglobin A1c may not be a reliable indicator of hyperglycemia in patients with SCD.[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,[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. [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.[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.[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.[3] Children and adolescents with SCD are frequently affected by delays in sexual maturation and late pubertal onset.[4,5]

These growth abnormalities are seen more commonly among children and adolescents with homozygous hemoglobin SS disease than among those with SCD.[6] There are several factors that contribute to growth delay and failure among children with SCD.[1,7,8,9,10] Infants and young children are particularly at risk for suboptimal nutritional intake during/following an acute illness.[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.[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.[13]

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