SICKLE CELL ANEMIA

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Introduction

Sickle cell anemia was first described by Dr. James B. Herrick of Chicago in 1910. Since that time the medical community's understanding of the disease has expanded, not always in a manner consistent with public awareness. Sickle cell anemia is a unique condition. The ultrastructural and biochemical basis for the disease has been identified. This, however, has not provided practical insights sufficient to effect a cure. Treatment is primarily supportive and conservative. Preventative measures are geared primarily to genetic counseling.

Sickle cell anemia is generally considered a disease of childhood. Few patients in the past survived into adulthood. Presently in the United States, an increasing number of cases are surviving into adulthood. The podiatric physician should be knowledgeable about sickle cell anemia and its complications. As patients with sickle cell anemia survive adolescence their foot problems will become more of a public concern. Patients with this disease can acquire a multitude of pedal afflictions such as may affect non involved persons. For this reason podiatrists need to be aware of the potential complications of the disease.

This report reviews the basics of pathophysiology, diagnosis, and lower extremity involvement in sickle cell anemia and sickle cell trait. A review and update of current knowledge is presented with emphasis on the podiatric manifestations and complications.

Pathophysiology

Herrick in 1910 was the first to describe the "peculiar elongated" and "crescent-shaped or sickle-shaped forms" of the red blood cells noted in this disease. Itano and Pauling in 1949 demonstrated an electrophoretically abnormal hemoglobin. Eight years later Ingram demonstrated that the hemoglobin in sickle cell anemia (HbS) differed from normal adult hemoglobin (HbA) by the substitution of one amino acid. Valine is substituted for glutamic acid at the sixth position on the two beta chains of the hemoglobin molecule.

The hemoglobin molecule is made up of four polypetide chains or subunits. There are two alpha and two beta chains each with an associated heme group. The synthesis of each subunit is governed by separate genes. Every individual possesses two genes to govern the formation of each polypetide chain, one from each parent. The genetics of sickle cell anemia follow classical autosomal dominance. If two heterozygous parents (sickle cell trait HbAS) have offspring, three statistically possible outcomes exist for the infant:

1. 25% chance of sickle cell anemia HbSS,
2. 50% chance of sickle cell trait HbAS,
3. 25% chance offspring will have normal hemoglobin genotypes HbAA.

This establishes the importance of genetic counseling for parents who may both be heterozygous for sickle cell anemia.

Eight percent of black Americans are heterozygous for HbS. Approximately 0.15% of black children in the United States have sickle anemia. The incidence of sickle cell anemia among adults is even less due to reduced life expectancy. Patients with sickle cell trait possess 33% HbS and 60% HbA. Children with sickle cell anemia possess a 75-95% HbS. The remaining 5%-25% of hemoglobin in children is fetal hemoglobin HbF.

The diagnostic tests for this condition are based on the presence of this combined hemoglobin, its concentration, and biochemical properties.

Individuals with sickle cell trait have few if any complications or symptoms. They are occasionally unaware that the gene has been passed to them from a parent. A sickle-cell crisis will only develop in these patients under extremes of hypoxemia. Such conditions can occur in the kidney and only rarely in other organs. The child with sickle cell anemia is prone to multiple organ complications and painful crises. No laboratory test or study can predict which children will have what organ problems or when or how many crises may occur in their lifetime.

The complications and organ damage occurs due to loss of pliability of the red blood cell and the increased viscosity of the blood. The sickled red blood cell is rigid and unable to distort and pass through the capillaries. The viscoid nature of the blood causes stagnation of flow in the capillary beds. Decreased oxygen tension promotes this sickled state.

The state itself promotes further sickling by further reducing oxygen tension within tissues. The tissues can undergo necrosis and fibrosis and this can affect every organ of the body.

Sickling can be reversible or irreversible. Irreversibility results from prolonged low oxygen states. Special blood sampling techniques such as the Sherman method can identify these cells. Any affected red blood cells containing HbS are mechanically fragile and easily hemolyzed in the circulation. This destruction of red blood cells results in hemoglobinemia, hemosiderosis, and urobilinogen in the feces and urine. The resulting hemolytic anemia remains fairly consistent in a given patient but can vary among a population of patients with sickle cell anemia. Hematocrit values range between 18 and 30 percent.

Clinical Presentation

The diagnostic screening tests for sickle cell anemia and sickle cell trait utilize the basic principle of mophogenic shape of the red blood cell to a reduced oxygen environment. When red blood cells of a sickle cell trait or anemic patient are placed on a slide and deprived of oxygen, the cells will eventually sickle. This slow process is expedited by the addition of metabisulfite to the slide. Solubility and mechanical precipitation tests can also be performed. False positives are possible and caused by non-sickle cell hemoglobin variants. These screening tests do not distinguish between sickle cell trait or anemia. Only the presence of HbS is needed for a positive result. The only method of definitive diagnosis is electrophoresis.

Electrophoresis can distinguish between sickle cell trait or sickle cell anemia. Double heterozygote disease, rare but possible with sickle C disease and sickle-beta-thalassemia, can likewise be diagnosed. The slightly altered electrochemical nature of the hemoglobin molecules from normal to sickle cell variants produces different hemoglobin electrophoretic patterns. The amount of HbS present is assessed to distinguish sickle cell trait from anemia. These patterns are diagnostic. This testing is important for patients who may express only mild forms of the disease and the diagnosis was not made during early childhood. No lab test can be utilized as a prognosticator of sickle cell disease. Other laboratory tests may demonstrate the multiple organ involvement of sickle cell anemia. For example, the patient may show signs and laboratory values consistent with jaundice and liver disease. Serum uric acid elevation and problems with gouty arthropathy may be present.

The symptom complex of sickle cell anemia is multifacetted depending on organ involvement. Generally, symptoms do not appear until sufficient fetal hemoglobin HbF has been replaced by sickle cell hemoglobin HbS. The increase in HbS occurs sufficiently to produce symptoms and clinical signs between the sixth month up to two years of age. The infant will show impaired growth and delayed development. The child will weigh less, be shorter, and possess thinner body type than children of comparable age. The adolescent and adult will appear gangling with long fingers and extremities. This body type has been described as eunucoid and arachnoid.

The sickle cell anemia patient has a significantly increased susceptibility to infection. Children and adults have a propensity for pneumonia. Osteomyelitis is many times more common in sickle cell anemia than in the general population. Gram negative organisms, salmonella in particular, is commonly identified. Osteomyelitis can be difficult to distinguish from the skeletal infarcts of sickle cell anemia.

Four types of acute sickle cell crises have been described. These include:

1. infarctive crisis,
2. hemolytic crisis,
3. aplastic crisis,
4. sequestration crisis.

Infarctive crises are the most common type. They are acutely painful and can affect any body part or organ system. Crises in the extremities can mimic osteomyelitis or gout. Both conditions can present in the sickle patient. Their identification is critical to establishment of supportive therapy. Joint pains in children can also mimic juvenile rheumatoid arthritis and misdiagnosis can easily occur. Besides the joints, the most commonly involved organ systems include the chest and gastrointestinal tract. Symptoms of abdominal pain have been confused with appendicitis and peritonitis.

Crises attacks may be widely separated or appear in clusters or close knit groupings. Many factors such as weather, climate, and activity have been described as inciting crisis situations. Crises are treated with hydration and analgesics. There seems to be a more positive correlation between relief of symptoms and initiation of treatment if treatment is instituted as soon as possible after the patient begins to experience pain. Careful monitoring of narcotic utilization is needed to prevent addiction and dependency. Many advances in such areas as antibiotic prophylaxis and supportive measures are being promoted to help in the chronic state as well.

Summary

This brief review of sickle cell anemia and trait is intended to refresh the podiatric physician's knowledge of this disease. A thorough review of the podiatric ramifications will be presented in the lecture format. The podiatric physician is important to the clinical management of the painful sequellae of sickle cell crises that may have occurred during childhood. Certainly the silent or mild sickle cell anemia should be considered in patients with family history of sickle cell anemia.

It is extremely important that the podiatrist be aware of the disease when present. Utilization of a tourniquet in the presence of sickle cell disease can produce anoxia of the limb and may lead to disasterous results.

Suggested Reading

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