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Dactylitis: A Complication in Patients With Sickle Cell Disease

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Abstract: Sickle cell disease (SCD) is a group of disorders that affects hemoglobin, the red pigment in blood erythrocytes responsible for delivering oxygen throughout the body. This is the most commonly inherited blood disorder. One of the most widespread manifestations of SCD is painful vaso-occlusive crises and osteomyelitis. Dactylitis or hand-foot syndrome is the first clinical sign of SCD among children under the age of 6 years, particularly for those aged 1-2 years. Sickle cell dactylitis, an acute vaso-occlusive condition is associated with pain and edema on the dorsum of hands or feet or both simultaneously, along with elevated local temperature and erythema. This review will detail the problems associated with the bone and skeletal involvement in SCD with specific emphasis on dactylitis in children; description of its signs, symptoms, effects, as well as treatment procedure.

Keyword: Dactylitis, Sickle cell disease, osteomyelitis, erythema

Introduction

Sickle cell disease (SCD) is an inherited chronic hematological disorder that affects millions of people across the globe.[1] This is the first monogenic disorder to be elucidated at the molecular level.[2] SCD is characterized by decreased or abnormal production of hemoglobin protein in red blood cells (RBC).[3] A normal adult hemoglobin mostly comprises of hemoglobin A (96-98%) which is made up of two alpha (α) globin chains and two beta (β) globin chains. The α-globin chain gene located on chromosome 16 is duplicated on each chromosome, hence α- chain is produced by four genes, whereas the β-chain lying on chromosome 11 has only one copy on each chromosome and is coded by two genes.[3] Genetic mutation in either α or β globin genes of hemoglobin A usually leads to hemoglobinopathy or hemoglobin disorders.

SCD is an autosomal recessive genetic disorder which arises from a single amino acid substitution of glutamic acid to valine at position 6 in the β-chain of hemoglobin. This mutation produces abnormal hemoglobin called hemoglobin S (HbS).[2] HbS polymerizes in the deoxygenated state leading to the formation of linear elongated fibers, which in turn cause physical deformation of RBCs by altering their biconcave shape to rigid sickle cell shape.[4] The average life span of sickle RBC is 12-16 days, which is nearly one-tenth of the life span of normal RBC.[5] These altered RBCs cannot efficiently pass through the microcirculation, and therefore obstruct the vasculature via a complex interaction of adhesive events among blood cells resulting in pain, anemia, and organ and tissue injury.[6] In fact, chronic hemolytic anemia and intermittent incidence of vaso-occlusion are the salient features of SCD.[5]

The clinical manifestation of SCD arises when both globin genes are abnormal resulting in homozygous HbSS or heterozygous such as β-thalassemia (HbS-thal) or hemoglobin C (HbSC). When a sickle β globin gene combines with a normal allele (HbSA), sickle cell trait occurs which is asymptomatic and does not require treatment. [7] The clinical phenotype of HbSS is extremely variable in spite of possessing the same genetic mutation, and is quite difficult to predict at an early age.[5] However, HbSS remains the frequent and most severe variant of SCD. Initial manifestation of SCD includes reduced function and degeneration of spleen, and dactylitis during

the first five years of life. Cerebral infarction was observed during first and second decade. Third and fourth decade of life shows gradual damage of the microvasculature, chronic end-stage failure of the organs such as the kidneys, lungs, brain, bones, gastrointestinal tract, and retina. This eventually deteriorates the quality of life and increases morbidity and mortality among adult SCD patients.[8]

Bones are considered to be the second most affected organs due to SCD, next to spleen. The sickle RBCs are found to accumulate in bone microcirculation leading to thrombosis, reduced blood flow, local hypoxia, infarction, necrosis, and acute painful crises.[9] In fact, painful vaso-occlusive crises and osteomyelitis are the most common complications of SCD, demanding hospitalization. The clinical and radiological manifestations of SCD are manifold; however, pathophysiologically all of them result from rigid adherent cells clogging small vessels, leading to tissue ischemia/infarction and gradual end-organ damage. Among several osteoarticular manifestations of SCD, dactylitis is frequently observed among children within the age of between 6 months to 6 years. This review discusses the clinical features and pathophysiology of dactylitis as well as the currently available therapeutic strategies for this complication.

Dactylitis

Dactylitis or hand-foot syndrome is generally the earliest clinical musculoskeletal manifestation of SCD that affects infants and young children in the age group of 6 months to 6 years, with highest incidence during the first 6-12 months of life.[3] In fact, affected infants normally do not develop symptoms in the first few months (0-4 months) of life due to the presence of fetal hemoglobin (Hbf) produced by the developing fetus, which prevents the RBCs from sickling. This Hbf is not present in the RBCs after 5 or 6 months of age hence, sickling of RBCs can occur from this age. Generally, children of the age of 1 to 2 years suffering from SCD show vaso-occlusive crises frequently in the small bones of hand and feet, which still contains hematopoietic bone marrow.[10] In fact, clinical data showed that before two years of age, the rates of occurrence of dactylitis are approximately 45% and the prevalence rate subsides at the age of 5-6 years due to the regression of red bone marrow with increasing age.[1,3] According to Stevens et al[11] nearly 50% of the children suffering from SCD develop dactylitis. A retrospective study carried out by Worrall and Butera[12] in United States reported that the incidence of hand-foot syndrome in children with SCD was 12%, and also observed that out of 16 patients, 55% showed dactylitis as the first sign of SCD.[9]

Dactylitis is mostly observed in patients with homozygous hemoglobin S disease (sickle cell anemia), sickle cell-hemoglobin C- disease or sickle cell- β- thalassemia.[13] However, a case report by Jadavji an Prodber[13] depicted the occurrence of dactylitis in a child with sickle cell trait. Moreover, dactylitis has been found to occur in SCD patients with lower Hbf and higher reticulocyte counts. The occurrence of dactylitis was also found to be associated with cold weather.[1]

The clinical symptoms of dactylitis in children include puffy, tender, warm feet and hands, acute pain, fever, reduction of movement, and refusal to bear weight.[13] Previous studies revealed different opinions regarding the role of dactylitis as a possible predictive factor of adverse outcomes. Studies conducted on Pediatric Cohort of Guadeloupe from 1984-1999[1] and a retrospective study by Miller et al[14] indicated that dactylitis occurring in children at an age less than 6 months could lead to severe consequences in later life, such as recurrent acute chest syndrome, stroke, frequent pain, and even death. On the contrary, the study on Dallas cohort by Quinn et al[15] could not reflect the importance of dactylitis as a possible predictor of adverse outcome, rather the study observed that those subjects predicted to be at high risk never experienced an adverse outcome and those predicted to be at low risk developed severe conditions later in life.

Sickle cell dactylitis in infants and young children is believed to be due to infarction or tissue necrosis at metacarpals, metatarsals, and phalanges, resulting from sickling of RBCs in the capillary beds and eventually blocking the vessels at these sites.[13] Histologically, extensive infarction of inner layer of the cortical bone,

medullary trabeculae, and the marrow results in enhanced erythropoiesis (production of erythrocytes or RBCs), sub-periosteal new bone formation, and bone marrow expansion of the hand and feet, causing swelling, tenderness, redness, and hyperthermia of the affected limb or digit.[1, 10] In fact, capillary blockage by abnormal sickle RBCs causes infarction in both the diaphysis and epiphysis of long tubular bones, leading to medullary infarcts and the appearances of a vascular necrosis respectively. Due to the impediment of blood through the bones and tissues, excruciating pain occurs, which is considered to be the classical painful bone crisis.[16] Furthermore, prolonged ischemia or infarction often led to bony destruction of the terminal phalanges and metacarpals.

In addition to the abnormal shape of RBC, there are several other factors affecting the blood flow in the vessels, which include viscosity of blood, the diameter of blood vessels, and various blood constituents. In general, SCD patients are prone to have increased blood viscosity that results in decreased flow of blood, which in turn hinders oxygen distribution to the essential areas of the body.[17] This tissue anoxia due to capillary stasis resulting from viscous blood is presumed to be another possible cause of sickle cell dactylitis.[13] Furthermore, swelling of soft tissue during dactylitis occurs due to the reparative response of hyperemia adjacent to the infarcted area and as the swelling subsides new periosteal bone is formed either through incorporation in to existing cortical bone or through layered deposits along the inner surface of the cortex.[3] This clinical condition is mostly observed in homozygous HbS disease, sickle cell hemoglobin C disease and sickle cell β- thalassemia.[13]

Dactylitis is manifested as self-limiting episodes which persist for one to two weeks and usually resolves within a month. Although it might relapse occasionally, it rarely leads to permanent joint sequelae.[9] However, in severe conditions high fever and enhanced white blood cell count (leucocytosis) could be detected. Dactylitis is often mistaken for osteomyelitis or juvenile arthritis due to similarities in symptoms.[13] Due to diagnostic imprecisions, management of these conditions sometimes becomes difficult.

Standard Radiography is usually performed to detect the disease. Radiographs are generally normal during the acute phase of vaso-occlusive crisis. However, the radiological changes could be observed 10 to 15 days after the onset of the syndrome.[18] Radiographs show areas of ill-defined translucency,[10] followed by patchy areas of sclerosis and lucency along with new periosteal bone formation in hand and feet, and soft tissue swelling of metacarpals or metatarsals. Within two to three weeks of the syndrome, radiographs reveal 'a moth-eaten' appearance of the involved digits, presumably due to cortical thinning, multiple irregular intramedullary deposits, and areas of spotty destruction.[18] Sometimes the small bones of the hand and feet took rectangular shape. Mostly the long bones are affected in dactylitis. Acute infarcts often lead to bone destruction or osteolysis and resultant deformity could also be observed.[3] However, infarction of epiphyses is very rarely associated with premature fusion and shortened fingers.[10]

Conservative treatment is considered to be the best treatment option for dactylitis, since symptoms generally subside by one to two weeks. In general, treatment is directed towards management and prevention of acute manifestations. Treatment involves bed rest, immobilization, use of topical heat pack to ease the discomfort and swelling. However, the use of cold or icepack should be avoided in order to prevent vaso-occlusive crisis. [19] The mainstay treatment for dactylitis includes use of oral or parenteral analgesics such as dipyrone, paracetamol, non-steroidal anti-inflammatory drugs for moderate pain and opioid derivatives for extreme painful crises.[9] A pain crisis can be prompted by preceding dehydration, infection, injury, or cold exposure. Hence, increased fluid intake to maintain proper hydration is extremely important and dehydration must be prevented to avoid further tissue injury. In fact, during extreme pain along with fever, aggressive intravenous hydration is necessary.[1] In order to treat co-existing infection antibiotic is prescribed. A previous study had also reported a significant reduction of dactylitis in very young children after the use of hydroxycarbamide.[1] Additionally, the use of hydxoyurea is highly recommended for pediatric SCD patients suffering from severe pain. Hydroxyurea stimulates the production of Hbf in blood. Hbf prevents sickling of the RBCs which is quite

useful for SCD patients. Besides Hbf production, hydoxyurea has several other benefits such as it decreases vaso-occlusive episodes and painful crises, increases the interval between the episodes of pain, and thus reduces the need for hospitalization or blood transfusion.[9] However, the response of hydroxyurea is varies from patient to patient and thus is unpredictable.

As a preventive measure, children suffering from dactylitis should avoid exposure to extreme cold and heat, especially cold, since severe cold causes peripheral vasoconstriction, and thus reduces the flow of blood through tissue vasculature and induces vaso-occlusive crisis.[20] It has also been noticed that administration of malarial prophylaxis could reduce both malaria as well as dactylitis episodes.[1]

Summary

SCD is a genetic disorder which involves multiple organs. Skeletal changes in SCD mainly results from hyperplasia of the bone marrow and vascular insufficiency resulting in thrombosis in microcirculation, which eventually leads to infarction and secondary infection. Dactylitis or hand-foot syndrome is a condition that causes tenderness, swelling, redness, and warmth of the affected hand or foot in infants and young children. This is the earliest musculoskeletal manifestation of SCD. The main radiological changes observed in bones are due to hyperplasia of the marrow and osteonecrosis. Although, dactylitis symptoms in some cases were misdiagnosed with arthritis or osteomyelitis, yet recent advancement in the diagnostic modalities are quite helpful in obtaining proper diagnosis. In addition, improvement of medical management is beneficial in reducing acute pain and swelling which in turn minimizes the morbidity in these patients.

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