REVIEW ARTICLE ISSN: 2249-3387

AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

SICKLE CELL DISEASE AND RELATED COMPLICATION

Saha Rajsekhar[1*], kuldeep Bhupendra[1], Bhatia G.S[1].

1. Chhattisghar Dental College and Research Institute, Rajnandgaon, Chhattisghar, INDIA.

ABSTRACT

A disease is so called the abnormal conditions that affect the body of an organism. It is usually treated as medical condition and respective support has to be providing to rescue the patient and to stop further physical damage. It may be caused by external factors, such as infectious disease, or it may be caused by internal dysfunctions, such as autoimmune diseases. In humans, disease is classified as to be any condition that causes pain, dysfunction, distress, social problems, or death to the person afflicted, or similar problems for those in contact with the person. In this broader sense, it sometimes includes injuries, disabilities, disorders, syndromes, infections, isolated symptoms, deviant behaviors, and atypical variations of structure and function, while in other contexts and for other purposes these may be considered distinguishable categories. There are four main types of disease such as pathogenic disease, deficiency disease, hereditary disease, and physiological disease. Diseases can also be classified as communicable and non-communicable disease. In the above article the complication related to sickle cell anemia have been illustrated, it's a sincere effort to summaries the vast complication in a single topic.

Key words: Sickle Cell Anemia, Sickle Cell Disorder, Sickling Complication, Sicklemia, Drepanocytosis**.**

*Corresponding Author Email: rajsekharsaha86@gmail.com.

Received 29 November 2011, Accepted 15 December 2011

Please cite this article in press as: Saha R *et al.*, Sickle Cell Disease and Related Complication. American Journal of PharmTech Research 2012.

INTRODUCTION:

Sickle-cell disease (SCD), or sickle-cell anaemia (or anemia, SCA) or drepanocytosis, is an autosomal recessive genetic blood disorder which bring out force full changes characterized by red blood cells that assume an abnormal, rigid, sickle shape. Sickling decreases the flexibility of the cell which results in a risk of various complications. The sickling occurs because of a mutation in the hemoglobin gene. Sickle cell trait (or sicklemia) describes a condition in which a person has one abnormal allele of the hemoglobin beta gene (is heterozygous), but does not display the severe symptoms of sickle cell disease that occur in a person who has two copies of that allele (is homozygous). Those who are heterozygous for the sickle cell allele produce both normal and abnormal hemoglobin (the two alleles are co-dominant). Sickle cell disease is a blood disorder in which the body produces an abnormal type of the oxygen-carrying substance hemoglobin in the red blood cells [1]. Sickle-cell disease, usually presenting in childhood, occurs more commonly in people (or their descendants) from parts of tropical and sub-tropical regions where malaria is or was common. One-third of all indigenous inhabitants of Sub-Saharan Africa carry the gene, because[2] in areas where malaria is common, there is a fitness benefit in carrying only a single sickle-cell gene (sickle cell trait). Those with only one of the two alleles of the sickle-cell disease, while not totally resistant, are more tolerant to the infection and thus show less severe symptoms when infected [3]. The prevalence of the disease in the United States is approximately 1 in 5,000, mostly affecting Americans of Sub-Saharan African descent, according to the National Institutes of Health [4]. In the United States, about 1 out of 500 African-American children born will have sickle-cell anemia [5]. Sickle-cell anemia is the name of a specific form of sickle-cell disease in which there is homozygosity for the mutation that causes HbS. Sickle-cell anemia is also referred to as "HbSS", "SS disease", "haemoglobin S" or permutations thereof. In heterozygous people, who have only one sickle gene and one normal adult haemoglobin gene, it is referred to as "HbAS" or "sickle cell trait". Other, rarer forms of sickle-cell disease include sickle-haemoglobin C disease (HbSC), sickle beta-plus-thalassaemia (HbS/β^{+}) and sickle beta-zero-thalassaemia (HbS/β^{0}). These other forms of sickle-cell disease are compound heterozygous states in which the person has only one copy of the mutation that causes HbS and one copy of another abnormal haemoglobin allele. The term *disease* is applied, because the inherited abnormality causes a pathological condition that can lead to death and severe complications. It have been also evidenced that the patients suffering from the disorder of sickle

cell anemia are sometime resistant to malaria and its parasite. Even the resistant from malaria have not over shadowed the complication created by the disease globally.

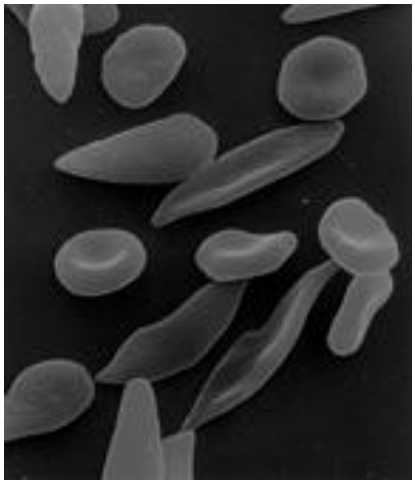

Figure 1. Normal and sickle-shaped red blood cells.

Pathophysiology

Sickle-cell anemia is caused by a point mutation in the β-globin chain of hemoglobin, causing the hydrophilic amino acid glutamic acid to be replaced with the hydrophobic amino acid valine at the sixth position. The β-globin gene is found on chromosome 16. The association of two wild-type α-globin subunits with two mutant β-globin subunits forms haemoglobin S (HbS). Under low-oxygen conditions (being at high altitude, for example), the absence of a polar amino acid at position six of the β-globin chain promotes the non-covalent polymerisation (aggregation) of haemoglobin, which distorts red blood cells into a sickle shape and decreases their elasticity [6]. The loss of red blood cell elasticity is central to the pathophysiology of sickle-cell disease. Normal red blood cells are quite elastic, which allows the cells to deform to pass through capillaries. In sickle-cell disease, low-oxygen tension promotes red blood cell sickling. The repeated episodes of sickling damage the cell membrane and decrease the cell's elasticity. These cells fail to return to normal shape when normal oxygen tension is restored. As a consequence, these rigid blood cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischaemia. The actual anemia of the illness is caused by haemolysis, the destruction of the red cells inside the spleen, because of their miss shape. Although the bone marrow attempts to compensate by creating new red cells, it does not match the rate of destruction [7].

Symptoms

Symptoms usually don't occur until after age 4 months. Almost all patients with sickle cell anemia have painful episodes (called crises), which can last from hours to days. These crises can affect the bones of the back, the long bones, and the chest. Some patients have one episode every few years. Others have many episodes per year. The crises can be severe enough to require a hospital stay [8].

Common symptoms include:

- Attacks of abdominal pain
- Bone pain
- Breathlessness
- Delayed growth and puberty
- Fatigue
- Fever
- Paleness
- Rapid heart rate
- Ulcers on the lower legs (in adolescents and adults)
- Yellowing of the eyes and skin (jaundice)

Other symptoms include:

- Chest pain.
- Excessive thirst.
- Frequent urination.
- Painful and prolonged erection.
- Poor eyesight/blindness.
- Strokes.
- Skin ulcers.

COMPLICATION RELATED TO SICKLE CELL DISEASE

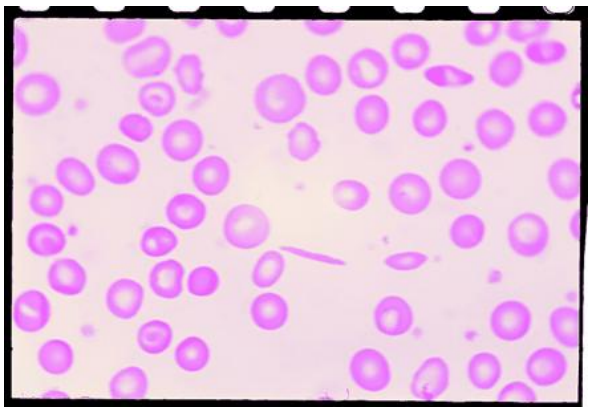

Figure 2. Characteristic sickle shaped erythrocytes in peripheral blood film of patient with homozygous sickle cell anemia.

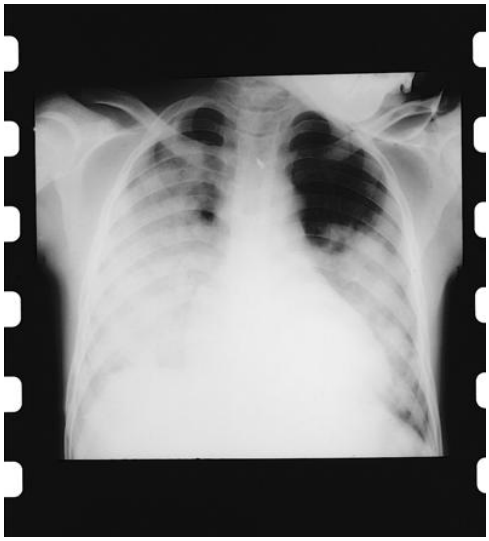

Figure 3. Acute sickle chest syndrome.

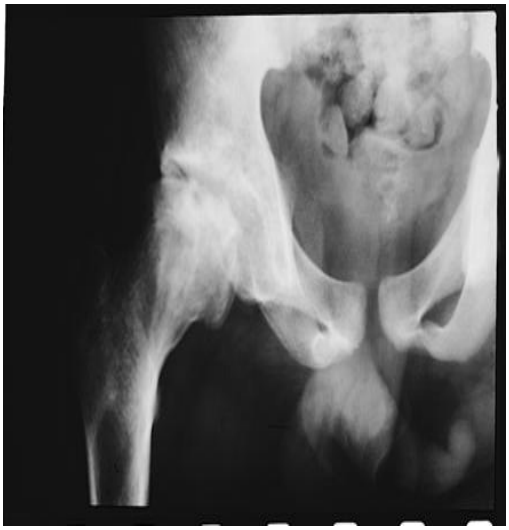

Figure 4. A vascular necrosis of femoral head in patient with heterozygous (hemoglobin SC) sickle cell anemia.

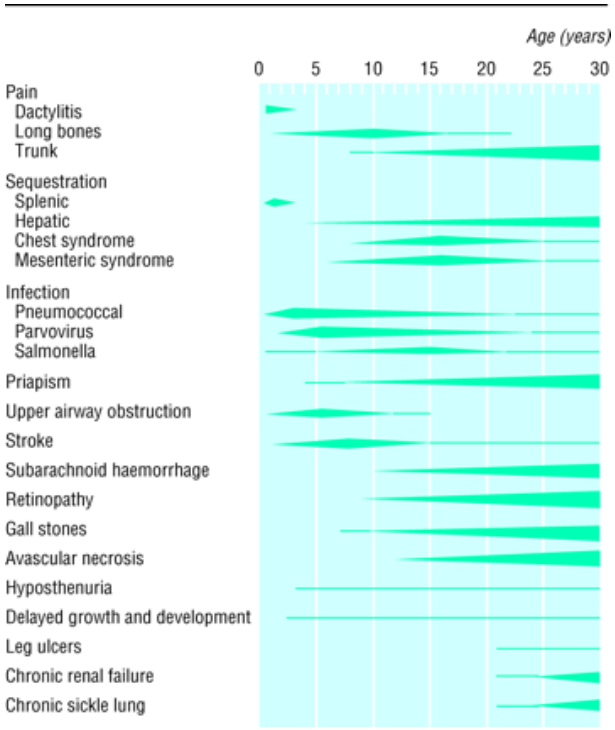

Figure 5. Clinical problems as per age in sickle cell disorder.

Cerebrovascular Accidents in Sickle Cell Disease (CVA)

Study of Sickle Cell Disease collected clinical data on 4,082 sickle cell disease patients enrolled from 1978 to 1988. The clinical data of the patients were collected for an average of 5.2 ± 2.0 years. Determination of age-specific prevalence and incidence rates of CVA in patients with the common genotypes of sickle cell disease were done and the effects of hematologic and clinical events on the risk of CVA were analyzed. The highest rates of prevalence of CVA (4.01%) and incidence (0.61 per 100 patient-years) were in sickle cell anemia (SS) patients, but CVA occurred in all common genotypes. The study concluded that, incidence of infarctive CVA was lowest in SS patients 20 to 29 years of age and higher in children and older patients. Conversely, the incidence of hemorrhagic stroke in SS patients was highest among patients aged 20 to 29 years. Condition for the ages in the mortality rate was 26% in the 2 weeks after hemorrhagic stroke. No deaths occurred after infarctive stroke. Risk factors for infarctive stroke included prior transient ischemic attack, low steady-state hemoglobin concentration and rate of and recent episode of acute chest syndrome, and elevated systolic blood pressure. Hemorrhagic stroke was associated with low steady-state hemoglobin and high leukocyte count [9].

Effects of Intramedullary Marrow Hyperplasia

The increased destruction of RBC result in the condition called anemia are the main stimuli for the persistence and subsequent expansion of red (hematopoietic) marrow. In a healthy adult, red

marrow is present only in the axial skeleton—the spine, sternum, pelvis, ribs, and proximal long bones. As the epiphyses develop and ossify, only yellow marrow is produced in them. The demand for increased production of red cells in sickle cell anemia stops the conversion to yellow marrow in the peripheral skeleton and leads to the persistence of appendicular red marrow throughout life. In infants with sickle cell disease, red marrow extends to all of the bones. With increasing age, it recedes from the small bones of the extremities (hands and feet) but persists in the ankles, wrists, and shafts of the long bones[10]. Osteoporosis of the skull vault may produce a granular appearance on radiographs. Vertical "hair-on-end" striations that project from the outer aspect of the vault also are seen [11]. Such striations are due to the prominence of trabeculae and to new bone formation. Although facial bones are not usually involved in marrow expansion in sickle cell disease, involvement of the mandible with osteopenia and coarse trabeculae is relatively common [12]. In the spine, cortical thinning and softening of bone produce a smooth biconcave deformity of the vertebral bodies: Adjacent intervertebral disks compress the endplates, giving the vertebrae the characteristic "fish-mouth" appearance.

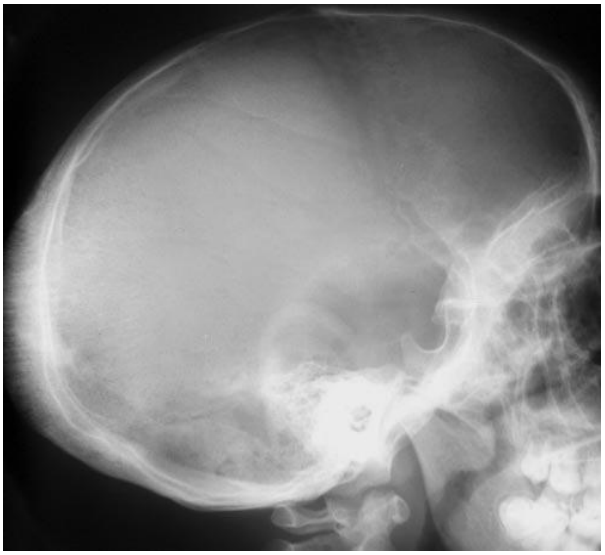

Figure 6. Bone marrow expansion within the skull vault. Lateral radiograph shows vertical hair-on-end striations in the occipital region. The medullary cavity is not widened.

Extramedullary Hematopoiesis

The above mention disorder is common in other blood related anemia such as Hb S–thal, extramedullary hematopoiesis occasionally is seen in sickle cell anemia. The most common site is the liver, but the spleen also may be affected, and soft-tissue hematopoietic masses may develop in the thorax, adrenal glands, and skin [13].

Thrombosis and Infarction of Bone

In infants and young children, infarction often occurs in the diaphyses of small tubular bones in the hands and feet. Infarction at these sites is termed sickle cell dactylitis or "hand-foot" syndrome[14] and results from the presence and persistence of red marrow in these regions. Severe pain at such infarcted sites is thought to be precipitated by cold-induced vasoconstriction. Sickle cell dactylitis is common between the ages of 6 months and 2 years but is rare after the age of 6 years because of the regression of red marrow in these areas with increasing age. Children often present clinically with tender and swollen hands and feet, reduction in movement, and fever. This syndrome occurs in approximately half of children with sickle cell anemia[15]. Both in children and in adults, the long bones are commonly affected. Acute infarcts cause osteolysis. The appearance of old bone infarcts depends on whether an adequate blood supply returns to the affected area. In areas of adequate revascularization, the scintigraphic appearance may return to normal after a few months. Other bones, such as the pelvis, ribs, and spine, may become markedly sclerotic because of medullary infarction as dystrophic medullary calcification occurs and new bone is laid down on infarcted bone. Infarction of the ribs in patients with sickle cell disease may contribute to painful chest crises with resultant hypoventilation and pulmonary infiltrates.

Epiphyseal Infarction

Epiphyseal ischemic necrosis in sickle cell anemia is common, frequently seen in the femoral and humeral heads, and more often bilateral than avascular necrosis in other diseases [16]. Patients who are symptomatic typically complain of joint pain and limited movement. About 50% of patients develop a vascular necrosis by the age of 35 years [17]. The contribution of synovial fluid to epiphyseal nutrition may offer some protection against infarction in children, among whom there is a lower prevalence of that complication (27%) [18]. As osteonecrosis progresses, changes become evident at radiography. Early radiographic signs include lucency and sclerosis within the epiphysis, subsequently, crescent-shaped subchondral lucencies develop and eventually, depression of the articular surface, collapse, and fragmentation occur. Changes may be seen in the acetabulum of the hip with osteophyte formation. In weight-bearing joints such as the hip, secondary degenerative changes are produced by altered mechanical factors following collapse. Collapse and secondary degenerative changes are less prominent features of osteonecrosis in non weight- bearing sites such as the humeral head.

Effect on Growth

Sickle cell anemia has a prominent effect on the growth of bone which is result from bone infarction. Epiphyseal shortening arises from vascular compromise, which causes damage to the growth plate, slowing or halting cartilage growth and leading to shortened bone [19]. Premature fusion of growth plates often occurs centrally because of the ingrowth of metaphyseal vessels, however, in tibiotalar slant deformity, premature fusion occurs laterally because of local ischemia. Epiphyseal deformities with cupping of adjacent metaphyses have been described in sickle cell anemia but also may occur in other childhood disorders, such as infection. In the spine, endplate depressions of the vertebral bodies are another manifestation of growth disturbance caused by ischemia and infarction. The H-shaped vertebral deformity is thought to be a result of central growth plate infarction. It can be distinguished from marrow hyperplasia by the characteristic sharp step like appearance of the vertebral endplate[20].

Septic Arthritis and Osteomyelitis

The major cause of hospitalization of the sickle patients are due to the infection of the bone and joints. In a study conducted regarding the assessment of above complication, resulted a relative rate of occurrence of almost 18% was found for osteomyelitis and 7% for septic arthritis [21]. The high frequency of infection in patients with sickle cell disease is due to a number of factors. Hyposplenism, which is secondary to infarction in childhood and subsequent fibrosis, is thought to be an important factor, as are impaired phagocytosis and complement dysfunction[22]. The admission of the patients in the hospital may lead to the exposure of various other microrganisums and pathogens such as various *Salmonella* species they are *S paratyphi B*, *S enteritidis*, *S typhimurium*, and *S choleraesuis.* Above mentioned are the most common bacterial pathogens linked to bone and joint infection in sickle cell disease and are thought to be implicated in most cases of osteomyelitis [23]. The next organism causing most of the bone infection in the sickle patients is *Staphylococcus aureus. Study conducted resulted to the fact that* approximately 10% of cases of sickle cell related osteomyelitis, in contrast to osteomyelitis from other causes, in which it is much more frequently a causal agent. Gram negative organisms also are implicated, and tuberculous osteomyelitis and arthritis have been reported in sickle cell disease [24,25]. Osteomyelitis regularly affects the long bones, but other bones, such as the vertebrae, also may be involved. The clinical manifestations are pain, fever, swelling, and increased inflammatory markers in blood serum. These clinical features are similar to those of painful bone crises, and differentiation of infection from infarction is difficult. In the above

condition the diagnosis of the complication is difficult and yet the treatment has to be done as early as possible.

Involvement of Muscles and Soft Tissues

Painful condition arises frequently in skeletal muscle and soft tissue alone, or they may also involve bone. Vasoocclusion may occur in muscle and lead to inflammation, edema, and myonecrosis. Fluid collections, hematomas, and fat necrosis may occur in soft tissue. Frequently, soft-tissue involvement is seen with bone infection. In osteomyelitis, associated fluid collections that communicate with marrow through cortical defects are seen. Foci of infection may arise in muscle and soft tissue without involving bone. Leg ulcers, particularly over bony prominences, are common in sickle cell disease as a result of venous stasis and tissue hypoxia. The organisms which are present in the skin and liable to cause infections may be monitored so that the condition of the skin ulceration or that wound may be treated [26, 27].

CONCLUSION

The sickle cell anemia is seen to be the most common genetic variation resulting to a number of complications such as cerebro-vascular accidents, hyperplasia, complicated haematopoisis, infarction, osteomyelities involving almost all parts of body. Sometimes leading to painful conditions by necrosis, vasoocclusions and few micro organisms exposed in severe conditions typically i.e. salmonella, staphylococcus and rarely mycobacterium species. This article is an effort to present the known complications related to sickle cell variations which come around the researchers. The above disease has been an issue in many communities, areas and parts of the world. Number of researcher are been involved in the work to bring out the various aspects factor related to the disease, but to have a cure the work have to be done in a large manner.

REFERANCES

1. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 330 (23): 1639–44.
2. Wellems TE, Hayton K, Fairhurst RM . The impact of malaria parasitism: from corpuscles to communities. J Clin Invest 2009; 119 (9): 2496–505.
3. National Heart, Lung and Blood Institute. Sickle cell anemia, key points. Retrieved 2010-11-27.
4. Ragusa et al. Presence of an African Beta-globin Gene Cluster Haplotype in Normal Chromosomes in Sicily. Am J Hematol 1992; 40:313-315.
5. Roach ES. Sickle cell trait: innocent until proven guilty. Arch. Neurol. 62 (11): 1781–2.

6. http://sickle.bwh.harward.edu
7. http://emedicine.medscrap.com/article/778971-overview.
8. http:// www. Sickle cell anemia-Pubmed Health.htm.
9. Kwaku Ohene-Frempong, Steven JW, Lynn AS, Scott TM, Stephen E, John WM, Doris LW, Charles HP, Frances MG. Cerebrovascular Accidents in Sickle Cell Disease: Rates and Risk Factors, Blood published by American Society of Hematology 1998; 91: 288-294.
10. Resnick D. Hemoglobinopathies and other anemias. In: Resnick D, ed. Diagnosis of bone and joint disorders. 4th ed. Philadelphia, Pa: Saunders, 2002; 2146–2187.
11. Sebes JI, Diggs LW. Radiographic changes of theskull in sickle cell anemia. AJR Am J Roentgenol 1979; 132:373–377.
12. Mourshed F, Tuckson CR. A study of the radiographic features of the jaws in sickle cell anemia. Oral Surg Oral Med Oral Pathol 1974; 37:812–819.
13. Gilkeson RC, Basile V, Sands MJ, Hsu JT. Chest case of the day. Extramedullary hematopoiesis (EMH). AJR Am J Roentgenol 1997;169:267, 270–273.
14. Babhulkar SS, Pande K, Babhulkar S. The handfoot syndrome in sickle-cell haemoglobinopathy. J Bone Joint Surg Br 1995; 77:310–312.
15. Stevens MC, Padwick M, Serjeant GR. Observations on the natural history of dactylitis in homozygous sickle cell disease. Clin Pediatr (Phila) 1981; 20:311–317.
16. Malizos KN, Siafakas MS, Fotiadis DI, Karachalios TS, Soucacos PN. An MRI-based semi automated volumetric quantification of hip osteonecrosis. Skeletal Radiol 2001; 30:686–693.
17. Styles LA, Vichinsky EP. Core decompression in avascular necrosis of the hip in sickle-cell disease. Am J Hematol 1996; 52:103–107.
18. Adekile AD, Gupta R, Yacoub F, Sinan T, Al Bloushi M, Haider MZ. Avascular necrosis of the hip in children with sickle cell disease and high Hb F: magnetic resonance imaging findings and influence of alpha-thalassemia trait. Acta Haematol 2001;105:27–31.
19. Siffert RS. The growth plate and its affections. J Bone Joint Surg Am 1966; 48:546–563.
20. Marlow TJ, Brunson CY, Jackson S, Schabel SI.Tower vertebra: a new observation in sickle cell disease. Skeletal Radiol 1998; 27:195–198.

21. Bahebeck J, Atangana R, Techa A, Monny-Lobe M, Sosso M, Hoffmeyer P. Relative rates and features of musculoskeletal complications in adult sicklers. Acta Orthop Belg 2004; 70:107–111.
22. Almeida A, Roberts I. Bone involvement in sickle cell disease. Br J Haematol 2005; 129:482–490.
23. Piehl FC, Davis RJ, Prugh SI. Osteomyelitis in sickle cell disease. J Pediatr Orthop 1993; 13:225– 227.
24. Burnett MW, Bass JW, Cook BA. Etiology of osteomyelitis complicating sickle cell disease. Pediatrics 1998; 101:296–297.
25. Kooy A, de Heide LJ, ten Tije AJ, et al. Vertebral bone destruction in sickle cell disease: infection, infarction or both. Neth J Med 1996; 48:227–231.
26. Sidhu PS, Rich PM. Sonographic detection and characterization of musculoskeletal and subcutaneous tissue abnormalities in sickle cell disease. Br J Radiol 1999; 72:9–17.
27. Feldman F, Zwass A, Staron RB, Haramati N. MRI of soft tissue abnormalities: a primary cause of sickle cell crisis. Skeletal Radiol 1993; 22:501–506.