Review

Osteoarticular complications of sickle cell disease in children

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Abstract

Introduction
Sickle cell disease is the most common molecular disease. The sickling of the haemoglobin S followed by micro-vascular occlusion leads to complications observable in several tissues. Osteoarticular complications represent the most frequent pattern of hospitalization of children with sickle cell disease. This review discusses osteoarticular complications of sickle cell disease in children.

Materials and methods
This study is a review concerning children <15 years of age. Phenotypes retained are SS, SC and AS, with or without thalassaemia or foetal haemoglobin. Osteomyelitis, arthritis and osteonecrosis are included. Ficat’s classification was used for osteonecrosis of femoral head.

Discussion
Osteomyelitis is the most frequent complication. It is classically due mainly to salmonella species, but currently, several studies have found other micro-organisms (Staphylococcus aureus, Streptococcus pneumoniae, klebsiella). Multiple sites are affected at the same time. Long bones are the most affected and according to studies, the most frequent are the humerus, the tibia or the femur. Delay to diagnosis often leads to chronic osteomyelitis, arthritis and osteonecrosis are included. Ficat’s classification was used for osteonecrosis of femoral head.

Conclusion
The osteoarticular complications must be hunted in children with sickle cell disease in order to diagnose them early. A quick and efficient treatment enables to avoid serious orthopaedic sequela.

Introduction
Sickle cell disease (SCD) is the most common and the first molecular disease identified. It is frequent in Africa, around the Mediterranean, in the Middle East, in the United States of America, in the West Indies and in Brazil. The prevalence is approximately 8% in African American. In Africa, the highest prevalence is found within the sicklemic belt of Lehmann, between the 15th North latitude and the 20th South latitude. In this belt, the prevalence of SCD is variable: 5-20% in West Africa and up to 40% in Central Africa. The abnormality is due to the substitution of a glutamic acid by a valine at the sixth position on the chain of β-globin, resulting in pathologic haemoglobin called haemoglobin S. This abnormality results from an autosomal recessive mutation on chromosome 11. The classic physiopathology of the SCD is based on the polymerization of haemoglobin S, followed by the sickling and dehydration of the red blood cell. The slowing down of blood circulation and obstruction of the micro-circulation by the deformed red blood cell are the primum movens of the manifestations of SCD. Three types of manifestations are seen in SCD: chronic haemolytic anaemia, vaso-obstruction phenomenon, and infections with a high sensitivity. The bone micro-circulation is a common place for red blood cell sickling, which leads to thrombosis, infarct and necrosis. The gravity of the SCD is naturally reduced by its association with α-thalassaemia and the persistence of foetal haemoglobin. The management of SCD and its complications, especially its osteoarticular complications, change from one country to another. It has been highly improved in developed countries in the last decades. In these countries, the medical follow-up is good; highly efficient techniques of medical imaging permit us to diagnose complications early, and treat them well and quickly, whereas in most African countries, the delay of consultation allows the worsening of complications.

This review aims at specifying the current situation of osteoarticular complications of SCD concerning their diagnosis, treatment and prognosis, and focussing on the differences between developed and developing countries.

Materials and methods
This study concerns children less than 15 years, having at least one haemoglobin S at haemoglobin electrophoresis. Any child with SS, SC or AS phenotype through electrophoresis

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of his haemoglobin was considered to be a sickle-cell child. These phenotypes can be or cannot be associated with thalassaemia or foetal haemoglobin.

The acute osteomyelitis was retained in the presence of bone pains, fever, efficiency of antibiotics and absence of chronic suppuration; the osteomyelitis was qualified chronic in the presence of sequestrum and/or fistula with chronic suppuration.

We called arthritis, the association of fever, pains, inability and swelling of the joints, with the presence of suppurative liquid in the joints cavity. When those manifestations are accompanied by epiphyseal bone modifications, they became osteoarthritic.

The aseptic osteonecrosis is a condition associating, in different stages, an osteoporosis, a geode and the deformation of the epiphysis without infection. We used Ficat’s classification for aseptic osteonecrosis of hip 13.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

The key event of manifestations of SCD is the sickling of the red blood cells, due to the polymerization of haemoglobin S, occurring in some conditions: deoxygenating, fever, dehydration, or long standing position 14,15. The sickling of red blood cells leads to vascular occlusion (especially capillary occlusion), and chronic anaemia by chronic haemolysis 14. The sluggish blood flow by sickle cells and the vascular occlusion explains the development of ischaemic focus 15. The chronic haemolysis results in the reduction of function of the spleen (functional asplenia) and liver; reduction of the reticuloendothelial system function; this suppresses the clearing of micro-organisms (especially salmonella) from blood, giving way to infections 16,17. The bone micro-circulation is a common place for the sickling of red blood cells; that is why the osteoarticular complications of SCD most frequently require hospitalization 18. They are often observed in the evolution of the disease, but in some cases, they are at the beginning and permit to discover SCD.

Apart from the painful vaso-occlusive crises (that will not be described in this paper), the main surgical osteoarticular complications of SCD are infections (acute and chronic osteomyelitis, aseptic arthritis or osteoarthritis) and aseptic or avascular necrosis.

Among the surgical osteoarticular complications of SCD in children, osteomyelitis is the most frequent, followed by arthritis and osteonecrosis. For Balogun et al. 15 osteomyelitis represented 37.4% of osteoarticular complications. In our service, the annual frequency was respectively 5.37% for osteomyelitis 9, 0.9% for septic arthritis of hip 16 and 0.7% for aseptic necrosis of femoral head 10.

Osteomyelitis

Osteomyelitis is the result of fixation and development of micro-organisms in bone marrow, thanks to the low blood flow in the bone 5. In addition, children with SCD are more susceptible to osteomyelitis than the rest of the children because of the sluggish blood flow in bones due to sickling of red blood cells 17. The intravascular sickling in gut vessels leads to capillary occlusion, devitalization and infarction of the gut, permitting salmonella invasion of blood 18,19. That is why high frequency of salmonella osteomyelitis in children with SCD in several studies is explained. However, the gut is not the only origin of micro-organisms in osteomyelitis during SCD. Skin wounds, infections of ear-nose-throat area, pneumonia or septicemia can be the origin of the micro-organisms. Salmonella is responsible for the osteomyelitis in children with SCD in more than 50% for Juliana and Muskett 20 and in over 70% for Onwubaliki 21. Salmonella has a high tropism for patients with SCD: in Saudi Arabia, salmonella infections are found in 11.5% of patients with SCD, against 0.65% of the general population 22. This report is not immutable; we think that apart from the special sensibility of salmonella with SCD patients, the bad hygienic life conditions of the concerning population can explain an endemicity of salmonellosis in some regions, especially in developing countries. Some studies from developed countries did not find salmonella: Lepage et al. 21 found decreased order Streptococcus pneumoniae, Hemophilus influenza and salmonella. The improvement of hygienic life conditions can keep away salmonella; that is why in some Nigerian studies 22–23, klebsiella was the first micro-organism, before salmonella. In Lomé (Togo), a former study 11 found salmonella as the first micro-organisms; but 8 years after, a new study in the same service 24 found Staphylococcus aureus first (22%) and salmonella second (19%). Others studies found staphylococcus as the first micro-organisms in osteomyelitis in SCD 25. The immunization against H. influenza makes these germs rare osteoarticular infections in children 26. Kingella Kingae now seems to be the second micro-organism after S. aureus in children less than 2 years old, but it needs special techniques to be found 27. Multiple taking (blood, bone puncture, joint liquid, skin wound) can permit us to identify the micro-organisms.

The osteomyelitis can be acute or chronic. It is well known that osteomyelitis has spectacular evolution in children with SCD, and acute

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osteomyelitis can quickly become chronic. An early diagnosis and quick treatment permits us to avoid this evolution in most cases. In that case, a radiograph at about 10 days shows linear bony apposition (Figure 1), which confirms the diagnosis of osteomyelitis. The admission delay plays an important role in the evolution; when it is short in developed countries (less than 3 days in 44% for Georgens et al.\textsuperscript{9}) it is often long in developing countries (in Lomé 6 days with extremes: 2 and 20 days for acute osteomyelitis). This delay can be longer for chronic osteomyelitis, with an average of 4 months in Lomé (Togo) (Figures 2, 3 and 4) and 7 months in Abidjan\textsuperscript{12}.

The frequency of chronic osteomyelitis decreases progressively when admission delay decreases. In Lomé, osteomyelitis was acute in 20 cases (46.51%) and chronic in 23 cases (53.49%)\textsuperscript{9}. However, 8 years prior to when these findings were reported, chronic osteomyelitis represented 75% of all cases\textsuperscript{14}.

The children with haemoglobin SS are often concerned with osteomyelitis, but every child who carries at least one haemoglobin S can develop osteomyelitis. In Lomé, among 43 children who developed osteomyelitis, there were 18 SS (41.86%), 14 SC (32.56%) and 11 AS (25.58%)\textsuperscript{9}.

All locations can be interested by osteomyelitis in children with SCD; but fertile metaphysis of long bones are often concerned. Long bones frequently develop pandiaphysitis (Figures 4, 5 and 6). It can also involve the short bones (Figure 7) and non-tubular bones. The favourite locations of infection vary from a study to another. In our study\textsuperscript{9}, the most frequent locations were on the humerus (28.57%), the tibia (19.05%) and the femur (14.29%). Al-Salem et al.\textsuperscript{17} in Saudi Arabia found in decreasing order the infections of the tibia, the femur and the humerus. A study carried on humeral osteomyelitis in children with and without SCD, permitted us to acknowledge that

**Figure 1:** Radiograph of the upper middle of the right leg in a boy of 4 years, SS: a linear bony apposition at the external edge of the tibia confirms the osteomyelitis.

**Figure 2:** Chronic osteomyelitis of the left tibia, in a boy of 6 years, AS. Admitted after evolution during 3 months, he had chronic suppuration and the almost entirety of tibial diaphysis was out.

**Figure 3:** (a) Chronic osteomyelitis of the right humerus in a girl of 15 years, SC. She had chronic suppuration by a fistula at the internal upper third of the arm. (b) Radiograph showed a sequestrum in the humerus.
two-thirds (66.67%) of the location was for children with SCD$^{27}$. Therefore, we concluded that every child admitted in Sylvanus Olympio Teaching hospital for humeral osteomyelitis (Figures 8 and 9) was likely two out of three times to suffer from SCD.

Multiple and sometimes symmetric locations characterize children with SCD$^{14,20}$. In our study, 43 children presented 63 locations: 57 on long bones and 6 on short bones$^9$ (Figures 10 and 11).

**Figure 4:** Acute pandiaphysitis of right humerus in a boy of 3 years, SS, with a pathological fracture at the upper metaphysic.

**Figure 5:** (a) Acute pandiaphysitis of the right tibia in a boy of 8 years, AS, with pathological fracture at the lower end (face view). (b) Acute pandiaphysitis of the right tibia in a boy of 8 years, AS, with pathological fracture at the lower end (profile view).

**Figure 6:** (a) Chronic pandiaphysitis of the left tibia in a boy of 10 years, SC (face view). (b) Chronic pandiaphysitis of the left tibia in a boy of 10 years, SC (profile view).
Acute osteomyelitis at the beginning can be difficult to differentiate from acute bone infarction. Clinical and haematological data may be subjective14. In those cases, combined technetium and galliumscintigraphy14, technetium sulfur colloid bone marrow scans15, and magnetic resonance imaging2,14,28 help to make the difference. At the magnetic resonance imaging, unenhanced T1 fat-saturated sequence leads to acute bone infarct, whereas contrast enhancement leads to acute osteomyelitis28. This enables a very early diagnosis of acute osteomyelitis and helps avoid empirical antibiotic therapy that can be abnormally applied to acute bone infarct. Nevertheless, the ‘sophisticated’ medical imaging is not available everywhere, especially in developing countries. In those conditions, we think that it is safer to treat acute bone pain occurring without obvious trauma, associated with fever in a child with SCD like osteomyelitis28. It is not safe for the patient, to wait for a sure diagnosis before beginning the treatment. The empirical treatment must be directed against salmonella and S. aureus. For that, we use ceftriaxone with netilmicin for 5-10 days, followed by ciprofloxacin orally, all for at least 6 weeks.

Chronic osteomyelitis characterized by long suppuration, by fistula (Figure 3-a) and sequestrum in bone (Figures 3-b, 6-a, 6-b and 9), can cause growth problems by destruction of the growth plate. They need some operations like removal of sequestrum and evacuation of suppuration. The growth troubles require long follow-ups and some complex orthopaedic surgery.

Arthritis

Many joints are concerned by arthritis in children with SCD. They are serious because in the absence of efficient and quick treatment, the affected joint can be definitely destroyed (Figure 12). They are often polyarticular and symmetric, with a predilection for large joints and lower extremities5. In the study by Balogun et al.16 it discussed the hip (40%), the knee (25%), the elbow (20%), the shoulder (10%) and the ankle (0.5%). The micro-organisms are generally the same as in osteomyelitis. In our study17, the hip arthritis had annual frequency of 0.9, and represented 52.94% of non-traumatic coxopathies in children with SCD. They studied nine children (with five phenotype SS, 2 SC and 2 AS) in 10 years. Their mean age was 6 years (extremes: 2 and 10 years). The arthritis was unilateral six times (Figure 13) and bilateral three times. They were due to salmonella in nine cases, and due to S. aureus in three cases. The early treatments with antibiotic therapy against salmonella and S. aureus, the immobilization, the puncture-drainage or the arthrotomy ensured the healing. In some cases, the delays of treatment or maladjusted antibiotic therapy led to osteoarthritis with destruction of the joint (Figure 14). In septic destruction of the joints, a bony revision interests both articular surfaces; in avascular osteonecrosis (AVON), bony revision interests the affected bone (Figure 15). The evolution of an osteomyelitis on an adjacent site to a joint can cause the infection of the joint, thus becoming osteoarthritis. The upper metaphysis of the femur being intra-capsular, the osteomyelitis of this segment is immediately
AVON in patients who had co-inherited alpha-thalassaemia trait (17% versus 34%). Phenotypes SS and SC are mainly affected: in our study of 14 cases, there were 8 SS and 6 SC. Femoral head is the most common site. Other joints like the knees and the small joints of the hands and feet or shoulders can be concerned. For 10 years, we have never seen in our service, the AVON of the knee or other joints in children with SCD. The AVON of the hip was only admitted, with annual frequency of 0.7. In the study by Balogun et al., all the 28 AVON affected the femoral head. The evolution is insidious and progressive and that explained the delay of diagnosis. Pains, limitation of the motion of the affected joints and occasionally pains at rest appear a long time after the beginning. Clinical manifestations are often late according to medical imaging signs, by especially standard radiograph. For Milner et al., more than 50% of patients had bilateral hip AVON (Figure 16). In our study, all the 14 patients had unilateral AVON of the femoral head (Figure 15). Eight were diagnosed at Ficat’s grade 3, and six at Ficat’s grade 4. In the study by Balogun et al., according to Ficat’s grades, on 28 cases, 20 were at grade 4, 7 at grade 3, 1 at grade 2 and 0 at grade 1. The early diagnosis is the best for prognosis; it is well done by magnetic resonance imaging, but not by standard radiograph. In developing countries, magnetic resonance imaging is not accessible for all. Therefore, we need to regularly follow up on our patients; the occurrence of abnormal pains in a hip, or at least changing in walking must lead to radiograph and CT scan. Without treatment, 87% of affected femoral head collapse within 5 years of diagnosis. The treatment is difficult. Nevertheless, it is better when the disease is discovered early. At early grade, bed rest can prevent the progression of joint damage. In addition, some authors proposed decompression coring procedure with beginning and radiograph can be normal. After a long evolution, radiograph can show bony revisions. The magnetic resonance imaging permitted by Adekile et al. found AVON of epiphyses in 27% of children with SCD. The AVON is rare in the first decade of life; the mean age of its onset was 35 years. In fact, we found in our study, a mean age of 14 years with extremes from 13 to 15 years. In a study by Balogun et al., on 15 patients less than 20 years old, only 2 were aged less than 10 years. Powers et al. found a lower frequency of the osteoarthrosis. The osteoarthrosis of the hip is very serious in small children because of a high risk of destruction of growth structures, femoral head and articular surfaces.

The arthritis can be associated with osteomyelitis (Figures 10-a and -b).

Aseptic osteonecrosis or AVON
The AVON occurs when a vaso-occlusion results in the infarction of the articular surfaces, and the head of long bones. The prevalence of the AVON in SCD is difficult to judge. The disease is asymptomatic at the beginning and radiograph can be normal. After a long evolution, radiograph can show bony revisions. The magnetic resonance imaging permitted by Adekile et al. found AVON of epiphyses in 27% of children with SCD. The AVON is rare in the first decade of life; the mean age of its onset was 35 years. In fact, we found in our study, a mean age of 14 years with extremes from 13 to 15 years. In a study by Balogun et al., on 15 patients less than 20 years old, only 2 were aged less than 10 years. Powers et al. found a lower frequency of the osteoarthrosis. The osteoarthrosis of the hip is very serious in small children because of a high risk of destruction of growth structures, femoral head and articular surfaces. The arthritis can be associated with osteomyelitis.

Figure 9: Chronic pandiaphysitis of the left humerus in a girl of 8 years, SS (face and profile views). Note the big sequestrum and the pathological fracture of the upper metaphysis.
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Figure 10: (a) Multiple and symmetric locations of osteomyelitis in a boy of 9 years, SS: all the coxa and the two femurs. Note the pathologic luxation of the left hip, worsening arthritis of the hip. (b) Multiple locations of osteomyelitis in a boy of 9 years, SS: osteoarthritis of the associated left knee. (c) Multiple locations of osteomyelitis in a boy of 9 years, SS: left femur.

osteotomy. The late grade requires a hip replacement, but with children, the arthroplasty must be postponed as later as possible. While waiting, the sphericity of the femoral head can be restored by injection in the femoral head, of acrylic cement or titanium. We have no experience with either the hip arthroplasty in children with SCD, or with the injection of acrylic cement or titanium.

Conclusion

Ostearticular complications worsen the life of children with SCD. Paediatricians must search hard for them and not wait for obvious signs. Acute osteomyelitis can be cured completely if it is diagnosed early and treated efficiently. Chronic osteomyelitis and septic arthritis can damage growth plates and joints, leading to serious orthopaedic complications. As for the AVON, their progressive and insidious evolution delays the diagnosis. During the follow-up of children with SCD, special attention must be given to the hips and the shoulders, in order to diagnose early a possible AVON.

References

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Figure 11: Multiple locations of osteomyelitis in a boy of 18 months, SSF2: two bones of the left forearm (a); bones of the right hand (b); bones of the left hand (c); bones of the right foot (d).

Figure 12: Osteoarthritis of the left elbow in a boy of 15 years, SS. Note the destruction of the articular surfaces and the disappearance of articular line.

Figure 13: Septic arthritis of the right hip in a boy of 3 years, AS, with a pathological luxation of the hip.
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Figure 14: Destruction of the left hip in a child of 9 years, SC, following hip arthritis. Entire lysis of the femoral head and neck, irregularity of acetabulum, and ankylosis.

Figure 15: AVON of the left femoral head, grade 3 of Ficat in a boy of 14 years, SS. Note that the acetabulum is still regular.


Figure 16: Bilateral AVON grade 4 of Ficat of both femoral heads, developing since 7 years in a boy of 25 years, SS. The participation of acetabulum after a long evolution of femoral head deformation without treatment should be noted.