



## Orthopaedic complications associated with sickle-cell disease

Antoine DE GHELDERE, Roger NDJOKO, Pierre-Louis DOCQUIER, Maryline MOUSNY, Jean-Jacques ROMBOUTS

*From the Cliniques universitaires Saint-Luc, UCL, Brussels, Belgium*

Sickle cell disease is the most frequent haemoglobinopathy in the world. It affects mostly African descent, but is also present in whites in Greece, Turkey, Italy and India. The responsible gene is autosomal co-dominant and only individuals homozygous for the gene are symptomatic. The condition is characterised by haemolytic anaemia crises and cardio-pulmonary, digestive, neurological, ocular and osteo-articular manifestations. Osteo-articular complications are frequent and may compromise harmonious growth.

This retrospective study reports the osteo-articular complications associated with sickle-cell disease encountered in our institution from 1975 to 2004. Orthopaedic complications were reported in 79 patients out of 325 who were followed with sickle-cell disease.

**Keywords** : sickle cell disease ; osteomyelitis ; septic arthritis ; avascular necrosis ; diaphyseal necrosis.

globin gene on chromosome 11. The mutant allele codes for the production of the variant haemoglobin : haemoglobin S (Sickle). The SCD mutation occurred in equatorial Africa and south-western Asia. The disease has now worldwide distribution due to population shifts, especially for southern Europe (7, 9).

The classical and most widespread genotype of SCD is the homozygous status (SS) coding exclusively for haemoglobin S production. The heterozygous carrier status (AS), known as sickle cell trait (SCT), results in production of both haemoglobin A and S and remains asymptomatic. Rare complications include increased susceptibility to heat exhaustion, splenic infarction at high altitude or after exercise, and, possibly, an increased incidence of renal tumours (5). Heterozygous genotypes

### INTRODUCTION

The first description of sickle-cell disease (SCD) was made in Chicago in 1910 by Herrick (10). In 1927, Hahn and Gillespie (6) showed that sickling of the erythrocytes was induced by deoxygenation and reversed with reoxygenation. Electrophoretic abnormalities of haemoglobin, which is the key for diagnosis, were demonstrated in 1949 by Pauling *et al* (14). SCD is currently the second most frequent genetic disease after Down's syndrome.

SCD is a hereditary haemoglobinopathy resulting from inheritance of a mutant version of the  $\beta$ -

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- Antoine de Gheldere, MD, Resident.
  - Roger Ndjoko, MD, Resident.
  - Pierre-Louis Docquier, MD, Orthopaedic Surgeon.
  - Maryline Mousny, MD, Orthopaedic Surgeon.
  - Jean-Jacques Rombouts, MD, Professor of Orthopaedics.

*Department of Orthopaedic Surgery, Cliniques universitaires Saint-Luc, Bruxelles, Belgium.*

Correspondence : Pierre L. Docquier, Department of Orthopaedic Surgery, Cliniques universitaires Saint-Luc, 10, avenue Hippocrate, B-1200 Brussels, Belgium.  
E-mail : Pierre-Louis.Docquier@clin.ucl.ac.be.

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coding for haemoglobin S together with other haemoglobin variants may result in symptoms of SCD. The most common heterozygous SCD genotypes are sickle-cell-haemoglobin C disease (AC) and sickle-cell- $\beta$  thalassaemia (S $\beta$ ). Haemoglobin C is a variant of haemoglobin A which is common in the African population (13).  $\beta$ -thalassaemias are a closely related group of haemoglobinopathies arising from a variety of mutations in the effector genes that regulate the expression of the  $\beta$ -gene. Individuals with the heterozygous sickle-cell- $\beta$  thalassaemia have thus decreased or absent production of haemoglobin A combined with expression of haemoglobin S, leading to symptoms of SCD.

Disease manifestations can be roughly attributed to two phenomena: haemolysis and vaso-occlusion. Haemolytic anaemia occurs in all forms of SCD and results from destruction of the sickled cells by monocytes and macrophages, from cell dehydration and direct membrane damage by rigid haemoglobin polymers (17). Vaso-occlusion is due to entrapment of sickled cells in the microcirculation and leads to tissue ischaemia and damage in almost all organs (17). The most frequent cause of hospitalisation in SCD is the acute painful crisis, which is most of the time transitory and occurs during the night. The average rate of vaso-occlusive crises (VOC) in the SS genotype is 0.8 per patient-year (15). The VOC can appear at different locations, resulting in varied complaints: haemarthrosis, epiphyseal avascular necrosis or diaphyseal infarction. Bone pain is thought to arise from cortical infarction or from marrow infarction that produces cortical pressure as a result of inflammation and oedema (16).

Fever is common during painful crises without documentation of infection and it mostly resolves without antibiotics (17). In children, painful crises often present as dactylitis of the hands and feet (hand-foot syndrome) and may result in premature closure of the affected epiphysis, leading to shortened and deformed bones. A frequent cause of hospitalisation and a leading cause of death is the acute chest syndrome (ACS). It is characterised by a new pulmonary infiltrate on the chest radiograph in a patient with either dyspnea, pleuritic pain, cough or

fever and often a fall in haemoglobin level (15). The aetiology is sequestration of sickled cells, fat embolism and thrombosis in the pulmonary vasculature. Overt stroke occurs in up to 11% of patients with SCD before the third decade of life and is one of the most devastating complications and a leading cause of death (15); it can be ischaemic or haemorrhagic. Renal dysfunction occurs to some degree in most forms of SCD and is a leading cause of death beyond the fourth decade (15). The spleen is one of the first organs affected in SCD (17). Hyposplenism makes patients susceptible to overwhelming infections with encapsulated micro-organisms such as *Streptococcus pneumoniae* (17). Bacterial infections (pneumonia and meningitis) are still a major cause of death in paediatric patients. Painful skin ulceration around the ankles is common in patients with homozygous SCD. Other important complications related to vaso-occlusion include priapism, avascular necrosis of the femoral head, myocardial infarction, sickle retinopathy and hyphaema, hearing loss (vaso-occlusion in cochlear structures) (17). Osteomyelitis occurs frequently, especially from *Salmonella* (17).

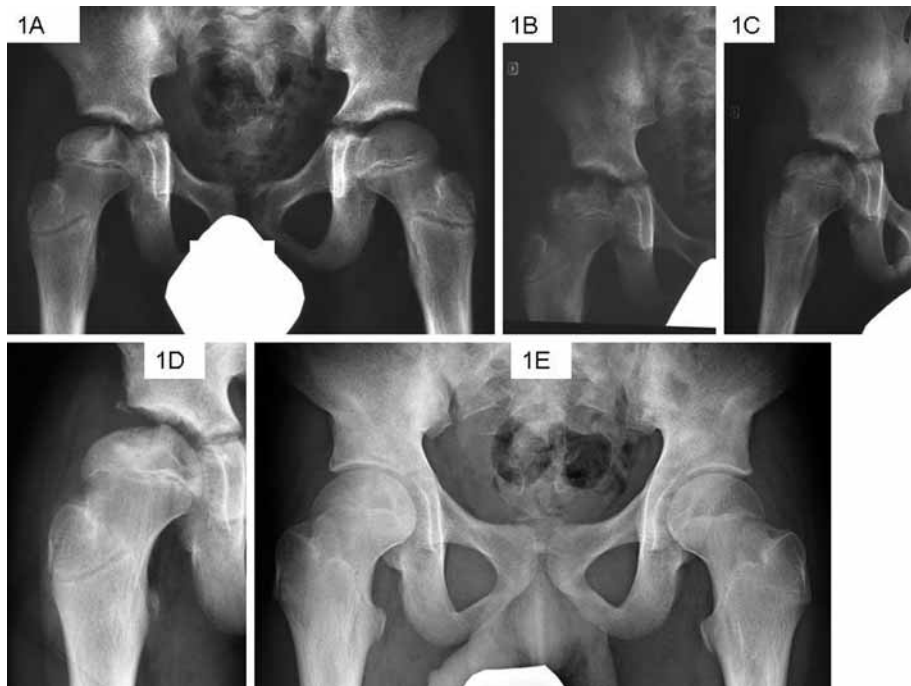
Diagnosis can be made by visualisation of sickled red cells on a routine peripheral blood smear but haemoglobin electrophoresis determines the presence of abnormal haemoglobins (17).

## PATIENTS AND METHODS

From 1975 to 2004, 325 patients with SCD have been followed up in our institution. There were 168 females and 157 males. There were 273 homozygous (SS) patients, 39 heterozygous (AS) and 13 composite heterozygous (SC, S $\beta$ ). Three hundred and nine patients were Africans (247 from the Democratic Republic of Congo), 15 were Italians (5 from Sicilia) and one was from India. These cases were retrospectively studied with focus on the orthopaedic complications.

## RESULTS

None of the heterozygous (SC, S $\beta$ ) patients had had symptoms of SCD. Orthopaedic complications were encountered only among the 273 homozygous (SS) patients.



**Fig. 1.** — A) Avascular necrosis of right femoral head in a 12 year 4 month-old boy treated with non weight bearing ; B) Fragmentation at 12 years 10 months ; C) Reconstruction at 13 years 5 months ; D) At 14-year follow-up ; E) Final result at 17 years 9 months.

### Diaphyseal necrosis

This complication was reported in 45 patients out of 273 (16%) with clinical and radiographic findings. The bones most frequently involved were the tibia in 13 cases (proximal tibia in 10), the femur in 11 cases (distal femur in 9) and the spine in 6. The other 15 cases showed a random distribution.

### Infections

Fifteen cases of infection were observed in the 273 patients with SCD (5%) : 3 with arthritis and 12 with osteomyelitis. The most frequent microorganism was *Salmonella sp.* (5 cases), followed by *Escherichia coli* (2 cases) and *Pneumococci* (1 case). No bacteria were cultured in the other 7 cases.

Frequent localisations of osteomyelitis were the tibia (4 cases), femur (2 cases) and spine (2 cases). No case was complicated by pathological fracture or chronic osteomyelitis. The two cases of septic

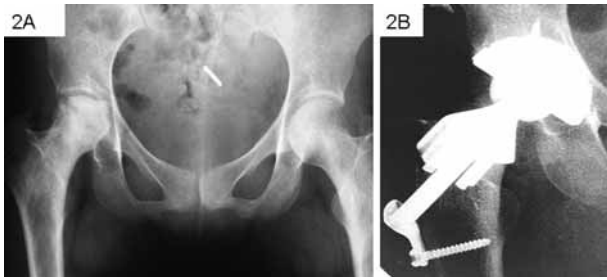
arthritis were located at the hip and knee respectively. No cases of myositis or fasciitis were encountered.

### Epiphyseal avascular necrosis

Twelve cases (4%) of *femoral head necrosis* were encountered in this series (fig 1). The sex ratio was 1:1. Necrosis was bilateral in 7 cases. Six cases (all female patients) went on to osteoarthritis of the hip at a mean age of 19 years. Two of them needed total hip arthroplasty (THA) at 16 years and 24 years of age respectively (fig 2).

Six cases of *humeral head necrosis* occurred. The sex ratio was 1:1. Necrosis was bilateral in 5 cases. One case evolved to glenohumeral osteoarthritis and needed shoulder arthroplasty. Humeral head necrosis was associated with femoral head necrosis in all 6 cases.

One case of necrosis of the medial femoral condyle was observed in a 42-year-old patient who developed osteoarthritis in the medial compartment of one knee and needed knee arthroplasty (fig 3).



**Fig. 2.** — A) Bilateral osteonecrosis of femoral head in a 24-year-old female. Right femoral head was collapsed while left femoral head was only condensed without collapse ; B) Total hip arthroplasty with Louvain-Hip prosthesis.

This patient had a history of bilateral necrosis of the humeral and femoral heads as well as knee septic arthritis with *Salmonella*.

## DISCUSSION

Osteo-articular manifestations of sickle-cell disease can be classified in acute and chronic. Possible acute lesions are hand-foot syndrome, diaphyseal infarction, acute osteomyelitis, haemarthrosis, infectious acute arthritis, gout arthritis, joint effusion and pathological fracture (7). Chronic manifestations are almost always the result of avascular osteonecrosis of the femoral head, humeral head and femoral condyle (7, 8). The most frequent chronic lesion is avascular osteonecrosis of the femoral head.

In our series, diaphyseal necrosis was seen most frequently. Necrosis is the next step after bone infarction, as a result of defective vascularisation of the diaphysis. The effect of lack of vascularisation



**Fig. 3.** — A) A 42-year-old male suffering from medial femoral condyle necrosis complicated with septic arthritis with *Salmonella* ; B) MRI showing large areas of necrosis in medial condyle as well in tibial and femoral metaphysis ; C) Total Knee Arthroplasty.



**Fig. 4.** — A) Hip arthrodesis for avascular necrosis of femoral head complicated with septic arthritis (*Salmonella*) just before desarthrodesis ; B) At 28 years : desarthrodesis with total hip arthroplasty ; C) At 35 years, loosening and fracture of acetabular component ; D) Revision of total hip arthroplasty.

is amplified by the poor venous drainage taking place in a bone swelling. Increased intramedullary pressure has been demonstrated in the child less than 10 years of age. In this series, the bones around the knee were those most frequently involved. Radiographic changes consisted of multiple cysts, periosteal reaction and sclerosis. Every case evolved to spontaneous bone reconstruction.

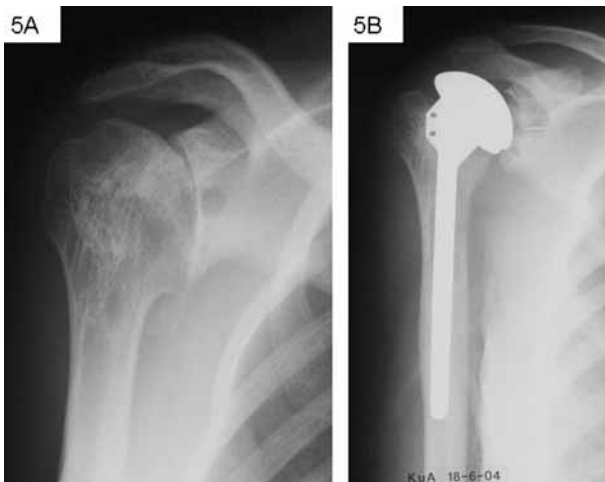
Infections often follow bone infarction. The poor vascularisation gives a perfect bed for infection. Infection can also be explained by hyposplenism, which diminishes the self-defence of the child. Most of the time, the pathogens come from the digestive tract : *Salmonella*, *Escherichia coli*, as in our series. In case of infarction, other micro organisms occur, such as *pneumococci*. In some cases, it is not easy to distinguish bone infarction from osteomyelitis (3, 4). Both are seen with low fever and blood CRP may be increased in both cases. If pain and fever are present, the rule is to consider radiographs and blood culture. The diagnosis was made by blood culture, aspiration if a collection was present or joint fluid culture.

In this series, infection was present in only 5% of cases, and was of the acute type in all cases. There were more cases with osteomyelitis than with arthritis. Osteomyelitis was treated by antibiotic and immobilisation. There was no need for bone resection or drainage. All of them did well follow-

ing conservative treatment. Arthritis, seen less frequently, was treated by antibiotics and arthrotomy. One case of hip arthritis was followed up in Africa : this patient presented joint stiffness of the hip following AVN, and eventually osteoarthritis. Hip arthrodesis was performed in Africa ; he subsequently underwent total hip arthroplasty in our institution (fig 4). The literature reports a higher incidence of infection, especially in African series, because of the poor sanitary conditions.

AVN of the femoral head in children has been well described, with three different stages. Stage 1 shows condensation, followed by fragmentation, and progresses to the final reconstruction stage (fig 1). The treatment is non-weight bearing, sometimes with traction. Stage 2 is the remodelling stage with produces coxa plana in more than 66% of cases, with some varus or valgus deformities. Stage 3 corresponds to the sequelae. The mean age for femoral head AVN is 12 years. As the remodelling phase is short compared to Legg-Calvé-Perthes disease, the prognosis is worse, with a frequent evolution to osteoarthritis for which the final treatment will be THA. In our series, no osteotomies were done in an attempt to prevent osteoarthritis of the hip.

AVN of the humeral head is rare, and is frequently associated with femoral AVN. Radiographic changes show irregular head deformities, caput



**Fig. 5.** — A) A 38 year-old-woman with omarthritis due to humeral head avascular necrosis ; B) Total shoulder arthroplasty.

magna or bone condensation with a normal head ; there are no structural changes at the glenoid. AVN of the humeral head is usually well tolerated, although in one case of our series, symptomatic omarthritis required total shoulder arthroplasty (fig 5).

Some patients have multiple avascular necrosis involvement. A 44-year-old female had bilateral femoral head necrosis, vertebral epiphysis necrosis, humeral head necrosis and tibial plateau and femoral condyle necrosis (fig 6).

Orthopaedic surgeons must be aware that SCD patients have a high incidence of perioperative problems. Perioperative complications can be specific to SCD or non specific. Specific complications include pain crisis and acute chest syndrome (ACS) occurring with a high frequency in the perioperative period (5). Older patients and pregnant women with SCD have an increased risk for perioperative morbidity (11). Non specific complications include fever, infection, bleeding, thrombosis, embolism, and death from causes other than SCD (5).

Common orthopaedic procedures reported include drainage of bone infections, joint replacement and correction of musculoskeletal deformities. Occlusive orthopaedic tourniquets are not contraindicated by SCD (1). In the study of Vichinsky *et al* (19), the patients undergoing hip replacements experienced the highest rate of complications with excessive intraoperative blood loss in the majority of patients and with SCD-related events (ACS and



**Fig. 6.** — A 44-year-old female with SDC. She also had sequelae of poliomyelitis with left lower limb paralysis. She has multiple necroses. A) Bilateral femoral head necrosis ; B) Typical aspect “H-letter” of the vertebrae due to necrosis of the vertebral epiphysis ; C) Necrosis of humeral head ; D) Necrosis of tibial plateau and femoral condyle.

pain crisis) in 19% of patients. Surgical complications occurred after 15% of 52 hip replacements and included postoperative haemorrhage, prosthesis dislocation, wound abscess and fracture of the femoral prosthesis (19).

Blood transfusion is by no means a risk-free therapy in SCD patients. Adverse effects include those of infection, including HIV which remains a major concern for patients in developing countries and Parvovirus B19 (predominant cause of aplastic crisis in SCD patients) (12). Patients are particularly prone to alloimmunisation to transfused red blood cell antigens. The incidence varies from 8 to 50% in patients with SCD (18). This may partly be the result of ethnic and racial differences between blood donors and SCD recipients. The presence of antibodies entails a risk to develop severe delayed haemolytic transfusion reactions. Antigen matching decreases the likelihood of alloantibody development and all transfused blood should be fully matched for Rhesus and Kell subgroups (12).

## CONCLUSION

SCD prognosis is still poor and management of related orthopaedic complications keeps challenging many surgeons. Survival estimation for homozygous (SS) patients reaches 45 to 55 years of age (20). Necrosis and infections are responsible for major functional impairment, and surgery has a place in the treatment of these complications.

Differential diagnosis between osteomyelitis and bone infarction is not always easy. Radiographs, blood culture and bacteriological culture of operative specimens are to be considered if possible (2). Hopefully, with better sanitary conditions we will see less cases of infection.

While waiting for new genetic therapy for SCD, the surgeon will treat the complications, preserving as much as he can the bone stock and keeping in mind that anaesthesia is more risky for these patients (5, 12).

## REFERENCES

1. **Adu-Gyamfi Y, Sankarankutty M, Marwa S.** Use of a tourniquet in patients with sickle-cell disease. *Can J Anaesth* 1993 ; 40 : 24-27.
2. **Chambers JB, Forsythe DA, Bertand SL et al.** Retrospective review of osteoarticular infections in a pediatric sickle cell age group. *J Pediatr Orthop* 2000 ; 20 : 682-685.
3. **Ebong WW.** Septic arthritis in patients with sickle cell disease. *Br J Rheumatology* 1987 ; 26 : 99-102.
4. **Epps C, Bryant D, Coles MJM et al.** Osteomyelitis in patients who have sickle cell disease. Diagnosis and management. *J Bone Joint Surg* 1991 ; 73-A : 1281-1292.
5. **Firth PG, Head CA.** Sickle cell disease and anesthesia. *Anesthesiology* 2004 ; 101 : 766-785.
6. **Hahn EV, Gillespie EB.** Sickle cell anemia. *Arch Intern Med* 1927 ; 39 : 233-254.
7. **Hernigou P.** Bone and joint manifestations of sickle cell anemia. *Acta Orthop Belg* 1999 ; 65 Suppl 1 : 9-16.
8. **Hernigou P, Bachir D, Galacteros F.** The natural history of symptomatic osteonecrosis in adults with sickle cell disease. *J Bone Joint Surg* 2003 ; 85-A : 500-504.
9. **Hernigou P, Galacteros F, Bachir D et al.** [Natural history of hip necrosis in sickle cell disease. A propos of 104 necroses]. (French) *Rev Chir Orthop* 1989 ; 75 : 542-557.
10. **Herrick JB.** Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. *Trans Assoc Am Physicians* 1910 ; 25 : 553-561.
11. **Koshy M.** Sickle cell disease and pregnancy. *Blood Rev* 1995 ; 9 : 157-164.
12. **Marchant WA, Walker I.** Anaesthetic management of the child with sickle cell disease. *Paediatr Anaesth* 2003 ; 13 : 473-489.
13. **Olson JF, Ware RE, Schultz WH et al.** Hemoglobin C disease in infancy and childhood. *J Pediatr* 1994 ; 125 : 745-747.
14. **Pauling L, Itano HA, Singer SJ et al.** Sickle cell anemia, a molecular disease. *Science* 1949, 110, 543.
15. **Platt OS, Brambilla BJ, Rosse WF et al.** Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med* 1994 ; 330 : 1639-1644.
16. **Rao VM, Fishman M, Mitchell DG et al.** Painful sickle cell crisis : bone marrow patterns observed with MR imaging. *Radiology* 1986 ; 161 : 211-215.
17. **Schnog JB, Duits AJ, Muskiet FAJ et al.** Sickle cell disease ; a general overview. *Neth J Med* 2004 ; 62 : 364-374.
18. **Vichinsky EP, Earles A, Johnson RA et al.** Alloimmunization in sickle cell anemia and transfusion of racially unmatched blood. *N Engl J Med* 1990 ; 322 : 1617-1621.
19. **Vichinsky EP, Neumayr LD, Haberkern C et al.** The perioperative complication rate of orthopedic surgery in sickle cell disease : report of the National Sickle Cell surgery Study Group. *Am J Hematol* 1999 ; 62 : 129-138.
20. **Wierenga KJ, Hambleton IR, Lewis NA.** Survival estimates for patients with homozygous sickle-cell disease in Jamaica : a clinic-based population study. *Lancet* 2001 ; 357 : 680-683.