bjh review

Bone involvement in sickle cell disease

Antonio Almeida and Irene Roberts

Department of Haematology, Imperial College London, Hammersmith Hospital, London, UK

Summary

Bone involvement is the commonest clinical manifestation of sickle cell disease both in the acute setting such as painful vaso-occlusive crises, and as a source of chronic, progressive disability such as avascular necrosis. Management of these problems is often difficult because of the diagnostic imprecision of most laboratory and imaging investigations and because of the lack of evidence for most surgical procedures in sickle cell disease. This review first discusses the acute problems related to bone involvement in sickle cell disease, with particular reference to differentiating infection from infarction, and then describes the long-term effects of sickle cell disease on bone mineral density, growth, and chronic bone and joint damage.

Keywords: sickle cell disease, bone, vaso-occlusion, osteomyelitis, osteonecrosis.

Acute bone problems in sickle cell disease

The most frequent complications requiring hospital admissions for patients with sickle cell disease are painful vaso-occlusive crises and osteomyelitis (Platt *et al*, 1991; Bailey *et al*, 1992; Neonato *et al*, 2000) (Table I). Other acute bony problems that have been described in sickle cell disease are stress fractures (Bahebeck *et al*, 2002), orbital compression syndrome because of orbital bone infarction (Ganesh *et al*, 2001; Naran & Fontana, 2001), dental problems (Demirbas *et al*, 2004), vertebral collapse (Emodi & Okoye, 2001) and bone marrow necrosis (Ataga & Orringer, 2000).

Vaso-occlusive crises

Vaso-occlusive crises affect virtually all patients with sickle cell disease, often beginning in late infancy and recurring throughout life. The pathogenesis of the microvascular occlusion, the hallmark of the painful sickle cell crisis, is complex involving activation and adhesion of leucocytes, platelets and endothelial cells as well as haemoglobin S-containing erythrocytes (Frenette, 2004). While this process can occur in virtually any organ, it is particularly common in the bone marrow, resulting in bone marrow infarction typically in the medullary cavity or epiphyses (Lonergan *et al*, 2001; Kim & Miller, 2002). The reasons for the vulnerability of the bone marrow to microvascular occlusion are unclear but may be partly because of marrow hypercellularity leading to impaired blood flow and regional hypoxia (Smith, 1996). Clinically, patients complain of intense pain localized to one or more areas of their skeleton. This may be accompanied by localized tenderness, swelling and erythema over the site of infarction; fever and leucocytosis are also common (Smith, 1996). Most patients recover from vaso-occlusive crises with no further complications. However, when marrow infarction involves the epiphyses, this may give rise to joint effusions that are clinically similar to septic arthritis (Smith, 1996; Kim & Miller, 2002), or where there is infarction of vertebral bone marrow, to collapse of the vertebrae with a typical 'fish mouth' appearance (Lonergan *et al*, 2001).

Dactylitis

In children under the age of 7 years, particularly those aged 1–2 years, vaso-occlusive crises frequently occur in the small bone of the hands and feet (dactylitis), which still contain haemopoietic bone marrow at this age in children with sickle cell disease (Kim & Miller, 2002). Clinically, dactylitis presents with acute, painful swelling of one or more of the digits. Histologically, there is extensive infarction of the marrow, medullary trabeculae and inner layer of the cortical bone, together with subperiosteal new bone formation (Weinberg & Currarino, 1972). Most episodes resolve within 2 weeks, by which time new bone formation is evident radiologically and there may be a 'moth eaten' appearance of the involved digits because of cortical thinning and irregular attenuation of the medullary spaces (Lonergan *et al*, 2001); rarely, involvement and infarction of the epiphyses leads to premature fusion and shortened fingers (Babhulkar *et al*, 1995).

Correspondence: Dr A. Almeida, Department of Haematology, Imperial College London, Hammersmith Hospital, Du Cane Road, London, UK. E-mail: antonio.almeida@breathe.com

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Table I. Acute bone problems in sickle cell disease.

Painful (vaso-occlusive) crisis
Osteomyelitis
Stress fracture
Orbital compression
Dental complications
Vertebral collapse
Bone marrow necrosis

Imaging during acute vaso-occlusive crises

The diagnosis of a painful crisis is predominantly a clinical one. Standard radiographs are generally not helpful in confirming the diagnosis of bone marrow infarction as they are usually normal during the acute phase of a vaso-occlusive crisis; although over the ensuing months radiographs often show areas of ill-defined translucency followed by arc-like subchondral and intramedullary lucent areas and patchy sclerosis (Lonergan *et al*, 2001).

By contrast, radioisotope bone scanning using a combination of ^{99m}technecium (Tc)-labelled sulphur colloid (to measure bone marrow uptake) and ^{99M}Tc-diphosphonate (to measure bone uptake) can reliably detect areas of infarction in the acute phase (Amundsen *et al*, 1984; Skaggs *et al*, 2001; Kim & Miller, 2002). This approach was used to show that infarcts in sickle cell disease can occur in every bone in the body (Kim & Miller, 2002). It also shows that the commonest sites for acute infarcts are the tibia/fibula (30%), the femur (25%) and the radius, ulna and humerus (21%), consistent with clinical data showing a predilection for the long bones (Keeley & Buchanan, 1982). Unfortunately, despite its sensitivity, radioisotope bone scanning has proved unreliable in distinguishing infarction from other complications such as osteomyelitis (see below) (Amundsen *et al*, 1984; Rao *et al*, 1985; Kim & Miller, 2002), and it is therefore not useful as a routine diagnostic investigation in sickle cell disease.

Magnetic resonance imaging (MRI) is also a very sensitive imaging technique for detecting bone and bone marrow infarction (Mankad *et al*, 1988; van Zanten *et al*, 1989; Mankad *et al*, 1990; Bonnerot *et al*, 1994; Deely & Schweitzer, 1997; Frush *et al*, 1999). Abnormal periosteal signal intensity and soft tissue changes are frequently seen in the first few days of a vaso-occlusive crisis; however, as with scintigraphy, these changes are often difficult to distinguish from those seen in osteomyelitis (Bonnerot *et al*, 1994; Frush *et al*, 1999). At present, therefore, MRI is not useful routinely in the management of patients with vaso-occlusive crises and should be reserved for investigating those patients whose symptoms fail to settle with conventional management and/or where there is a high suspicion of osteomyelitis. Similarly, as discussed below, there are difficulties both with MRI and scintigraphy in distinguishing between infarction/infection and infarction/increased marrow haemopoiesis in sickle cell disease (Keeley & Buchanan, 1982; Deely & Schweitzer, 1997).

Osteomyelitis

The increased susceptibility of sickle cell disease patients to infections, including osteomyelitis, has long been recognized with several mechanisms postulated including hyposplenism, impaired complement activity and the presence of infarcted or necrotic bone. A recent French study of a cohort of 299 patients followed in four Parisian centres, found a prevalence of osteomyelitis of 12%. Interestingly, the prevalence was significantly lower in those patients with the Bantu haplotype (Neonato *et al*, 2000). This finding is in keeping with other studies where it was found that patients with more severe haplotypes such as Benin and Senegal, not only have more severe organ damage because of sickling, but also have increased incidence of infectious complications (Padmos *et al*, 1991).

The most common cause of osteomyelitis in sickle cell disease is *Salmonella* (especially the non-typical serotypes *Salmonella typhimurium*, *Salmonella enteritidis*, *Salmonella choleraesuis* and *Salmonella paratyphi B*), followed by *Staphylococcus aureus* and Gram-negative enteric bacilli (Atkins *et al*, 1997; Burnett *et al*, 1998), perhaps because intravascular sickling of the bowel leads to patchy ischaemic infarction (Table II). Osteomyelitis in sickle cell disease has also been reported in association with tuberculosis (Kooy *et al*, 1996) and systemic spread of *Mycobacterium ulcerans* from a Buruli skin ulcer (Pszolla *et al*, 2003).

Diagnosis of osteomyelitis in sickle cell disease

Diagnosis of osteomyelitis can be one of the most common management dilemmas in sickle cell disease: failure to identify it may result in severe bone damage and life-threatening infection while an erroneous diagnosis subjects the patient to at least 6 weeks of unnecessary intravenous and oral antibiotics. Osteomyelitis usually presents with pain, swelling and tenderness over the affected area. The most common sites are the femur, tibia or humerus (Stark *et al*, 1991). Most patients also have fever and elevated inflammatory markers (Chambers *et al*, 2000; Skaggs *et al*, 2001) but the fever may be modest (Bennett, 1992). These signs and symptoms are similar to those found in vaso-occlusive crises, making the distinction between a painful crisis and osteomyelitis extremely difficult on clinical grounds; indeed osteomyelitis may not be suspected until the

Table II. Causes of osteomyelitis in sickle cell disease.

Salmonella typhimurium
Salmonella enteritidis
Salmonella choleraesuis
Salmonella paratyphi B
Staphylococcus aureus
Haemophilus influenzae
Escherichia coli
Enterobacter spp.

signs and symptoms of a typical painful crisis have failed to resolve after 1–2 weeks of standard therapy (Jean-Baptiste & De Ceulaer, 2000). Blood cultures are often sterile when taken at this stage, as it is common practice to treat patients with vaso-occlusive crises with broad-spectrum antibiotics upon admission, especially if they are febrile. Thus, confident diagnosis of osteomyelitis in such patients tends to rely on various imaging techniques. However, in some cases, osteomyelitis presents late, as a more indolent process often with abscess formation, in which case there is usually little diagnostic difficulty (Barrett-Connor, 1971; Dirschl, 1994).

On plain radiographs, the changes seen at the early stages of osteomyelitis, namely periostitis and osteopenia, are non-specific and also seen in vaso-occlusion and therefore of limited value (Lonergan *et al*, 2001). Lucent areas are not seen until much later in the natural history of the infection (Fig 1). Ultrasonography shows the extraosseous pathology in acute osteomyelitis and may show periosteal elevation (William *et al*, 2000). It has also the advantage of being rapid, non-invasive and fairly simple to target to the area(s) of maximum pain (Sidhu & Rich, 1999). The sensitivity of ultrasonography in diagnosing osteomyelitis in sickle cell disease has been reported to be as high as 74% (Rifai & Nyman, 1997; Sadat-Ali *et al*, 1998; William *et al*, 2000; Riebel *et al*, 2003). However, as with computer tomography (Stark *et al*, 1991), the main 'diagnostic' finding (subperiosteal fluid) is not specific and can also be present during vaso-occlusive crises, although greater fluid depths (>4 mm) are reported to be highly associated with a diagnosis of osteomyelitis (William *et al*, 2000).

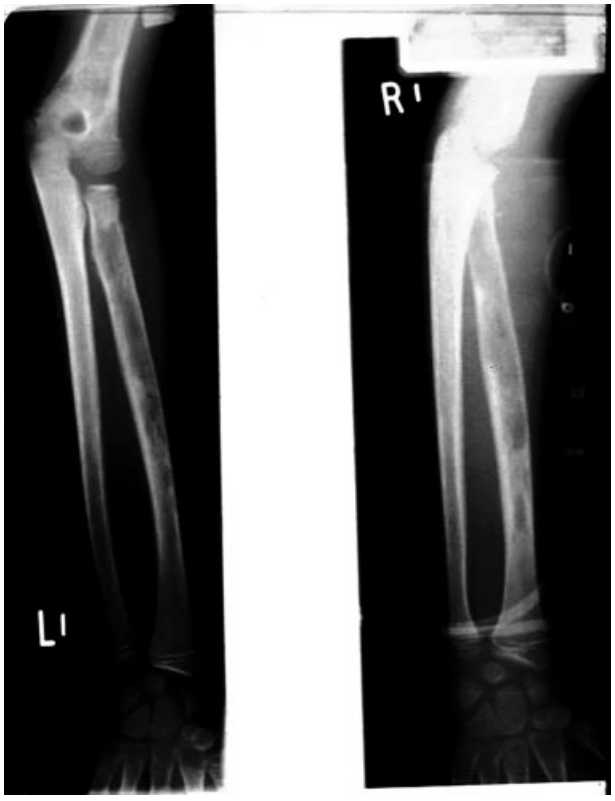

Fig 1. Multifocal osteomyelitis showing lucent areas of infection in the radii.

As mentioned above, radioisotope bone scanning is also reliable in distinguishing osteomyelitis from infarction with confidence in sickle cell disease (Amundsen *et al*, 1984; Rao *et al*, 1985; Crowley & Sarnaik, 1999; Kim & Miller, 2002). A combination of ^{99m}Tc-sulphur colloid and ^{99M}Tc-diphosphonate (Buchanan, 1996; Skaggs *et al*, 2001; Kim & Miller, 2002) or ^{99M}Tc with gallium seems to improve accuracy (Amundsen *et al*, 1984), as marrow uptake tends to be normal in osteomyelitis while it is usually increased in infarction; however, as both false positives and false negatives still occur, we no longer use this approach. Radiolabelled leucocyte scans similarly fail to reliably discriminate between osteomyelitis and infarction (Buchanan, 1996).

The MRI is increasingly being used to help diagnose osteomyelitis (Lonergan *et al*, 2001). As with other imaging modalities, there is overlap between the changes seen in infection and infarction: in both situations MRI shows reactive marrow oedema together with surrounding hyperaemia (Bonnerot *et al*, 1994; Umans *et al*, 2000). The accuracy of MRI is greater when gadolinium enhancement is used (Deely & Schweitzer, 1997; Umans *et al*, 2000) but even this is not 100% specific for differentiating osteomyelitis from infarction (Frush *et al*, 1999; Lonergan *et al*, 2001). However, once osteomyelitis was confirmed by culture results, it is very useful for accurate localization of the lesion and for monitoring for response to treatment once antibiotic therapy has been initiated (Bonnerot *et al*, 1994).

Therefore, despite the progress made in the development and use of imaging techniques, a definitive diagnosis of osteomyelitis in sickle cell disease still relies more upon clinical assessment together with positive cultures from blood or bone obtained by aspiration or biopsy, than upon any single imaging modality. It is also useful to remember that bone pain in sickle cell disease is much more likely (in one series (Keeley & Buchanan, 1982) it was 50 times more likely), because of a vaso-occlusive crisis than to osteomyelitis.

Treatment of osteomyelitis in sickle cell disease

The choice of antibiotics is generally dictated by the microorganism detected. Our first line treatment for confirmed or suspected osteomyelitis is a third line cephalosporin such as ceftriaxone, in order to make sure *Salmonella* infections are covered. Ciprofloxacin is a useful alternative for older children with *Salmonella* osteomyelitis, having the advantage of excellent oral bioavailability. In adults, other species such as *Staphylococcus*, should also be covered by empirical antibiotic therapy (Sadat-Ali, 1998). Treatment of confirmed cases should continue for at least 6 weeks.

When there is radiological evidence of accumulation of fluid at the site of infection, drainage is recommended (Sadat-Ali, 1998). However, there is no firm consensus

regarding when to drill or drain and these invasive procedures tend to be reserved for those who are not responding to antibiotic therapy or those who have localized encapsulated septic collections (Syrogiannopoulos *et al*, 1986; Atkins *et al*, 1997; Sadat-Ali, 1998).

Septic arthritis

Septic arthritis is also seen in sickle cell disease and is generally caused by the same organisms as osteomyelitis (Ebong, 1987). It rarely develops in isolation; instead, it tends to occur in association with a painful vaso-occlusive crisis (Jean-Baptiste & De Ceulaer, 2000). Early diagnosis to prevent irreversible joint damage is essential but usually not problematic because of the ease with which diagnostic synovial fluid can be obtained. It is, however, important to be cautious as vaso-occlusion affecting the articular surfaces may lead to a similar clinical picture as infectious arthritis (Jean-Baptiste & De Ceulaer, 2000).

Other acute bone problems in sickle cell disease

Bone involvement in sickle cell disease may also contribute to other sickle-related complications. In acute chest syndrome, both rib infarcts, leading to hypoventilation because of pain and fat embolism, secondary to bone marrow infarction, are important contributory factors in the pathogenesis of the syndrome (Rucknagel, 2001; Salzman, 2002). Other acute bony problems that have been described in sickle cell disease include stress fractures (Bahebeck *et al*, 2002), vertebral collapse (Emodi & Okoye, 2001) and orbital compression syndrome because of orbital bone infarction, which may present with acute periorbital swelling (Ganesh *et al*, 2001; Naran & Fontana, 2001). Dental problems are particularly prevalent in patients with sickle cell disease. There is an increased incidence of dental caries (Laurence *et al*, 2002), pulpal necrosis (O'Rourke & Hawley, 1998; Demirbas *et al*, 2004; Kavadia-Tsatala *et al*, 2004) and abnormal radiographic and morphological findings (Taylor *et al*, 1995). Compounded with the relatively poor blood supply to the mandible, it is not surprising to find an increased incidence of mandibular osteomyelitis in sickle cell disease secondary to dental infections (Adekeye & Cornah, 1985; Olaitan *et al*, 1997).

Chronic bone problems in sickle cell disease

Chronic skeletal problems are common in sickle cell disease (Table III). Many patients suffer from chronic pain because of avascular necrosis (AVN), vertebral collapse and/or chronic arthritis. In addition, hyperplasia of the bone marrow may cause osteopenia and growth disturbance (Claster & Vichinsky, 2003).

Table III. Chronic bone problems in sickle cell disease

Osteonecrosis
Chronic arthritis
Osteoporosis
Impaired growth

Avascular necrosis

Osteonecrosis or AVN, occurs when vaso-occlusion results in the infarction of the articular surfaces and heads of the long bones. The true prevalence of osteonecrosis in sickle cell disease is difficult to judge because of the small number of prospective studies using sensitive methods of detection such as MRI (Ware *et al*, 1991; Adekile *et al*, 2001; Gupta & Adekile, 2004). However, by using MRI, Ware *et al* (1991) found osteonecrosis in the epiphyses of almost 41% of adults with sickle cell disease. Adekile *et al* (2001), also using MRI, found a slightly lower prevalence in children (27%). These studies both showed a much higher frequency of osteonecrosis than previously reported in studies based on plain X-rays. Milner *et al* (1991) studied 2590 patients and found radiological evidence of osteonecrosis of the femoral head in only 9·8% of patients with sickle cell disease, with the highest frequency in adults, in those with homozygous sickle cell disease and in those with co-existing alpha-thalassaemia trait. That this is an underestimate of the true prevalence of osteonecrosis is also suggested by the finding that 47% of patients with hip disease and 79% of those with shoulder disease were asymptomatic at the time the radiological diagnosis was made (Milner *et al*, 1991).

A recent cohort study over four decades in 284 patients with sickle cell disease found that osteonecrosis was present in 15% of the cohort (Powars *et al*, 2002). The mean age of onset was 35 years and it was rare in the first decade of life (Powars *et al*, 2002). However, as the authors acknowledged, this study probably underestimated the true frequency of osteonecrosis in sickle cell disease, as there was no systematic screening of asymptomatic patients and a higher frequency of osteonecrosis was found in the more recent decades when MRI became available (Powars *et al*, 2002). This study also found a lower frequency of osteonecrosis in those patients who had co-inherited alpha-thalassaemia trait (17% vs 32% patients without alpha-thalassaemia trait) although this was not found in other studies in sickle cell disease (Steinberg *et al*, 1983) or sickle cell disease in general (Ballas *et al*, 1989; Milner *et al*, 1991).

The pathophysiology of osteonecrosis in sickle cell disease seems to differ from osteonecrosis because of other aetiologies. When MRI is used to quantify lesions in AVN of the femoral head, the lesions seen in sickle cell disease are larger than those seen in osteonecrosis because of other aetiologies (Malizos *et al*, 2001). Whereas in osteonecrosis not because of sickle cell disease, the localization and size of the lesions is directly related to the mechanical stresses on the femoral head, the larger size and wider distribution of the lesion in sickle cell disease point to the fact that a much larger variety of independent factors result in vascular occlusion in sickle arthropathy.

The most common sites of osteonecrosis are the femoral heads followed by the head of the humerus, knee and small joints of the hands and feet (Jean-Baptiste & De Ceulaer, 2000; Lonergan *et al*, 2001). It is common to have multiple joints affected: >50% of patients with an affected hip have bilateral disease and 74% of those with an affected shoulder will also have AVN of the femoral head (Milner *et al*, 1991; Milner *et al*, 1993).

Symptomatic patients complain of painful, limited motion of the affected joint, occasionally with pain at rest. Advanced disease may be easily diagnosed with plain radiographs, which show mottled attenuation of the epiphysis, subchondral lucent areas and flattening/collapse of the articular surfaces (Fig 2). This may be followed by narrowing of the joint space, articular sclerosis and osteophyte formation (Lonergan *et al*, 2001). Early disease is best diagnosed by MRI as mentioned above, plain X-rays may not detect early disease (Milner *et al*, 1991; Gupta & Adekile, 2004). Untreated, 87% of affected femoral heads will collapse within 5 years of diagnosis (Hernigou *et al*, 2003).

The treatment options for AVN of the hip in sickle cell disease are difficult to assess as no controlled trials comparing the different approaches are published. One of the most effective methods of preventing progression of joint damage is bed rest, in order to avoid weight bearing (Hernigou *et al*, 2003), however, this has such drastic implications for patients' lives that it is usually an unacceptable option. In addition, the long-term symptomatic treatment is ineffective and the majority of joints require surgery for pain relief and functional improvement. Early disease may improve with coring and osteotomy (Styles & Vichinsky, 1996); however, failure rates in some studies are as high as 50% at 5 years (Bishop *et al*, 1988; Clarke *et al*, 1989; Milner *et al*, 1991) and a randomized controlled trial is currently in progress to determine whether decompression coring procedures can prevent progression of AVN (Claster & Vichinsky, 2003). Late disease requires joint replacement. Such patients must be cared for in specialized centres with expertise in sickle cell disease as they have a very high incidence of perioperative complications (compared with general orthopaedic patients), including excessive blood loss, acute chest syndrome, infection and failure of prostheses (Vichinsky *et al*, 1999). Other surgical techniques (Hernigou *et al*, 1993) are being used in an attempt to overcome these problems but none have yet produced satisfactory results.

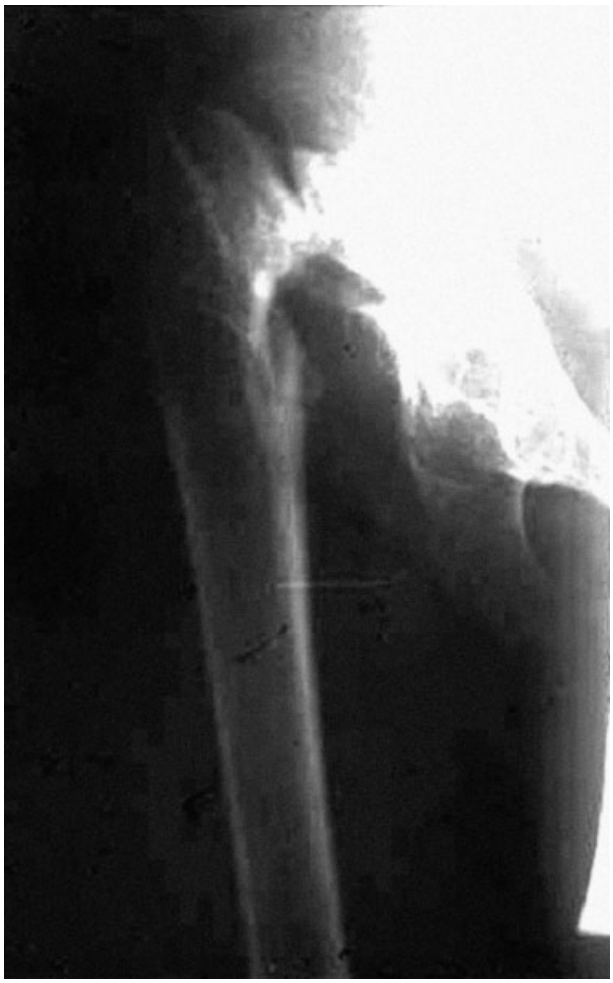

Fig 2. Avascular necrosis of the right hip with destruction of the femoral head.

Osteopenia and osteoporosis

Several studies have shown an overall reduction in bone mineral density, attributed to marrow hyperplasia, in patients with sickle cell disease (Brinker *et al*, 1998; Soliman *et al*, 1998; VanderJagt *et al*, 2002; Nelson *et al*, 2003). Compared with normal subjects from the general population, Brinker *et al* (1998) found that the patients with sickle cell disease had lower bone mineral density values in all scan regions (*c.* 6–21% lower than expected). In particular, vertebral osteoporosis is common in patients with sickle cell disease (Brinker *et al*, 1998). Radiologically, this shows as increased radiolucency of the vertebral bodies, prominence of vertebral trabeculae and a smooth, biconcave deformity of the vertebrae known as 'fish-mouth' vertebrae, which forms as a result of compression by the adjacent intervertebral discs (Williams *et al*, 2004a). Patients may go on to develop vertebral collapse either from the osteoporosis or as a result of vertebral infarction. Vertebral collapse is often asymptomatic but may cause acute and/or long-term pain requiring analgesia and mechanical support such as a brace.

Growth

Impaired growth is a well recognized complication of sickle cell disease in children (Platt *et al*, 1984; Stevens *et al*, 1986; Leonard *et al*, 1998; Barden *et al*, 2002); at least some of this impairment in growth seems to be because of marrow hyperplasia (Claster & Vichinsky, 2003). Marrow hyperplasia can cause ischaemia of the central portion of the vertebral growth plate, leading to disturbance of vertebral growth and resulting in the characteristic 'H' shaped vertebrae because of squared-off depression of the vertebral end plates (Reynolds,

1987; Williams *et al*, 2004a). Alternatively, some female patients with sickle cell disease develop 'tower' vertebrae in which there is an increase in the height of the vertebral bodies without an associated increase in the girth, again postulated to be a consequence of chronic marrow hyperplasia (Marlow *et al*, 1998). In addition to marrow hyperplasia, local anoxic events may lead to premature closure of epiphyses and impaired or even asymmetrical growth of the long bones of the limbs (Collett-Solberg *et al*, 2002).

In addition to these marked skeletal abnormalities in the spine, there is also evidence of more subtle abnormalities as a common feature of sickle cell disease. A recent study carried out a detailed assessment of growth, nutritional status and body composition in 36 children with homozygous sickle cell disease (Barden *et al*, 2002). There was no significant difference in their height or bone age between the children with sickle cell disease and their age, sex and ethnically matched controls. However, the sickle cell disease group had significantly delayed skeletal maturation and had marked deficits in *z*-scores for weight-for age, height, elbow breadth, skin fold thickness and mid upper arm circumference, consistent with global deficits in growth and energy reserves (Barden *et al*, 2002). Growth hormone deficiency is a reversible cause of impaired growth but not commonly seen in these children (Nunlee-Bland *et al*, 2004). Several studies have shown that children with sickle cell disease have lower levels of vitamins A, B6 and D than their ethnically matched peers and that these levels were related to these children's morbidity (Nelson *et al*, 2002; Schall *et al*, 2004). In addition, vitamin deficiencies in sickle cell disease do not seem to be related to malnutrition *per se* (Kennedy *et al*, 2001) but to a high resting energy expenditure, which also seems to be related to the degree of impaired growth in these children (Odonkor, 1983; Williams *et al*, 2004b).

Conclusion

The vast majority of complications affecting patients with sickle cell disease are musculoskeletal in origin and, although they do not contribute significantly to mortality, they are the major source of acute and chronic morbidity. Despite their significant clinical and socioeconomic impact, the resources available to diagnose and treat bone disease in sickle cell disease remain limited. The use of hydroxycarbamide has significantly altered the quality of life of those with recurrent vaso-occlusive crises but the treatment of acute crises remains largely supportive (Amrolia *et al*, 2003). Similarly, the management of osteomyelitis remains problematic, as current imaging techniques fail to confidently distinguish between osteomyelitis and vaso-occlusion often leading to long hospital stays and invasive investigations before a definitive diagnosis can be made. Of the chronic bone disorders, the most disabling is osteonecrosis. Management of this condition is generally unsatisfactory; despite the availability of early diagnosis, no strategy other than absolute bed rest has yet been shown to prevent progression of joint damage and surgery is associated with a high rate of postoperative complications. Finally, it is clear that most, if not all patients with homozygous sickle cell disease have abnormal skeletal growth and maturation; the mechanisms and implications of this for the health of children and adults with this disease remain to be explored.

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