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Review

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Haemoglobinopathies and the rheumatologist

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Abstract

The haemoglobinopathies are a relatively common, heterogeneous group of inherited conditions that are the result of either a quantitative abnormality (e.g. thalassaemia) or structural [e.g. sickle cell anaemia (SCA)] of the globin part of the haemoglobin molecule. Musculoskeletal (MSK) complications are common in patients with haemoglobinopathies and may affect the whole of the MSK system, in addition to bone, which is the primary site of the disease. Typical MSK complications include painful vaso-occlusive disease and osteomyelitis in SCA and reduced BMD in thalassaemia. Patients may also develop a number of related (e.g. gout) or unrelated rheumatic diseases (e.g. inflammatory arthritis and autoimmune CTDs). Treatment of MSK conditions in patients with haemoglobinopathies may be challenging (e.g. bone marrow suppression from disease-modifying agents) and in particular in SCA, steroid therapy (by any route) may precipitate potentially severe vaso-occlusive complications. Rheumatologists need to be aware of the range of MSK complications, treatment challenges and the need for such patients to be managed as part of a dedicated multidisciplinary team alongside haematology.

Key words: haemoglobinopathies, sickle cell anaemia, sickle cell disease, thalassaemia, musculoskeletal, infection, bone, arthritis, gout, muscle

Rheumatology key messages

- Musculoskeletal involvement is common in patients with haemoglobinopathies.
- Rheumatologists should consider other rheumatic diseases (e.g. RA) in patients with haemoglobinopathies and musculoskeletal symptoms.
- Treatment may be hazardous, even life-threatening, in patients with haemoglobinopathies, in particular, steroid therapy in sickle cell anaemia.

Introduction

Musculoskeletal (MSK) symptoms are common in patients with haemoglobinopathies. The purpose of this review is to highlight the range of rheumatological complications that may occur in patients with haemoglobinopathies. In particular, it is important that rheumatologists are aware of the possibility of the presence of related (e.g. gout) and unrelated rheumatic diseases (e.g. inflammatory arthritis and autoimmune CTDs), because both the prognosis and the treatment may differ significantly. This review will focus on the MSK complications observed in sickle cell anaemia (SCA) and thalassaemia major because these are the most common haemoglobinopathies to be encountered by rheumatologists in routine clinical practice.

Haemoglobinopathies

Haemoglobin is a tetramer, consisting of two α-like and two β-like globin chains. The haemoglobinopathies are a group of inherited disorders of the globin portion of haemoglobin [1]. The two main types of haemoglobinopathies result from either a quantitative reduction in globin chain output (thalassaemias) or a tendency for the haemoglobin molecules to polymerize [sickle cell disease (SCD)]. They are the commonest monogenetic disorders worldwide, with an estimated carrier

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prevalence of ~7%, mainly in sub-Saharan Africa, South East Asia and the Western Pacific [1–4].

In general, the treatment of haemoglobinopathies is usually supportive rather than curative. Chronic blood transfusions results in iron overload in the major organs, necessitating the use of iron-chelating agents [1, 2].

Thalassaemia syndromes

α-Thalassaemias

Most people have four functioning α-globin genes, and α-thalassaemia (minor) trait occurs when one or two of these genes are mutated or deleted. It is an asymptomatic condition. Haemoglobin H disease results from a single functioning α-globin gene, resulting in an excess of free β-globin genes, which form tetramers (HbH). It presents with haemolytic anaemia, moderate splenomegaly and resultant erythroid bone marrow expansion. The most severe form of α-thalassaemia is haemoglobin Bart's (hydrops fetalis), which is due to a near or complete absence of functioning α-globin genes and usually results in fetal death [1, 2].

β-Thalassaemias

β-Thalassaemia results from mutations in one or both of the β-globin genes (chromosome 11), causing either the absence or insufficient production of the β-globin chains [1, 4]. β-Thalassaemia minor occurs when a mutation in the β-globin gene is inherited from one parent, causing mild asymptomatic anaemia [1, 4]. β-Thalassaemia intermedia results from the inheritance of two mild β-thalassaemia mutations, which can cause significant anaemia and splenomegaly [1, 4]. β-Thalassaemia major is due to the inheritance of two severe thalassaemia mutations and results in a severe reduction or absence of β-globin synthesis [1, 4]. Symptoms include anaemia, failure to thrive, growth retardation, marrow hyperplasia, marrow expansion (including frontal bossing) and massive splenomegaly [1, 2].

SCD

SCD is caused by a mutation in codon 6 of the β-globin gene, changing glutamic acid to valine in the resulting globin chain [5]. Haemoglobin incorporating this mutated globin chain is called sickle haemoglobin (HbS) and has a tendency to polymerize in the deoxygenated state. SCA, the most severe form of SCD, is caused by homozygous inheritance of HbS from both parents. Other compound heterozygote states exist, most notable HbSC disease, in which HbS is coinherited with HbC (glutamic acid mutated to lysine in codon 6 of the β-globin gene). HbSC disease is typically less severe than SCA [5]. Median life expectancy is 50–60 years, with increased childhood mortality in sub-Saharan Africa due to *Haemophilus* and pneumococcal infections as a result of loss of ability to eradicate encapsulated organisms [2, 5]. Important infective organisms in SCA are *Salmonella* spp. (including *choleraesuis*, *enteritidis*, *paratyphi B* and *typhimurium*), *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Gram-negative enteric bacilli* and *Mycobacterium tuberculosis* [5]. *Mycobacterium tuberculosis*, in particular, should be considered in the differential diagnosis of osteomyelitis. Heterozygosity for HbS (sickle cell trait) confers a protective survival advantage against infection with malaria [2].

In conditions of low oxygen tension, HbS polymerizes, rendering the red blood cell membrane more rigid. After recurrent cycles of sickling, there is an eventual failure to return to the natural (biconcave) state [5, 6]. Sickled red blood cells occlude the microcirculation, resulting in tissue ischaemia and infarction [5]. Common triggers for sickling include hypoxia, fever, infection, dehydration and acidaemia [1, 5].

Blood transfusions control the severity of anaemia and reduce the risk of complications [5]. Penicillin prophylaxis and vaccination against *Haemophilus* and pneumococcal species are indicated. Hydroxycarbamide has been shown to reduce the frequency of acute pain and acute chest syndrome as well as potentially reducing organ damage and death [7].

MSK manifestations of the haemoglobinopathies

The major MSK complications of the thalassaemias and SCA are summarized in Table 1.

Painful vaso-occlusive disease

Episodes of painful vaso-occlusive disease of bone (sickle cell crises) are characteristic of SCA, but may also involve the soft tissues, including muscle. Bone infarction occurs in the medullary cavity and epiphysis, resulting in vaso-occlusive crises and avascular necrosis [8]. The primary pathophysiological process involves vaso-occlusion of postcapillary venules, with resultant bone infarction and subsequent inflammation [1, 9]. An example of severe knee bone infarcts (with severe degenerative joint disease) in a patient with SCA is depicted in Fig. 1.

In a prospective study of 3578 patients with SCA, the reported prevalence of painful vaso-occlusive episodes was around one (0.8) episode per patient year; however, there was a wide variation noted, with some patients experiencing multiple episodes [10]. In those patients with SCA who had more frequent painful episodes, there was an increased risk of death observed [10].

Patients typically present with acute severe pain, often described as a dull ache, with swelling of the affected area and tenderness to palpation of the infarcted bone. In adults, the limbs are most often affected, and multiple sites can be involved. In children, the hands and feet are most commonly affected, with swelling (dactylitis) of the digits or with more extensive bony involvement (e.g. of the carpal bones), often called the hand–foot syndrome (Fig. 2). Shortening of the digit secondary to dactylitis is well recognized (Fig. 2). It is often clinically very challenging to distinguish between acute vaso-occlusive pain and osteomyelitis. Krishnamoorthy *et al*. [11] report a case of primary hyperparathyroidism mimicking painful vaso-occlusive disease in a child with SCA, with an

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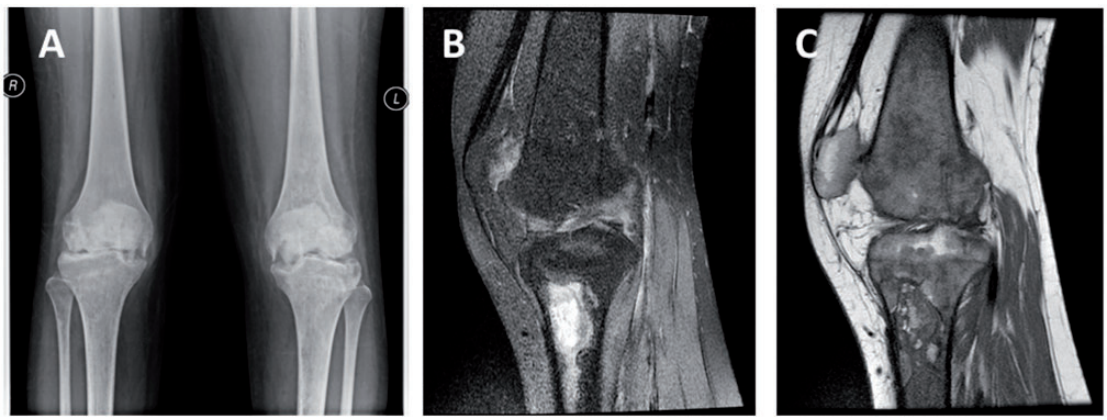
Table 1 The musculoskeletal complications of the thalassaemias and sickle cell anaemia (note that this is not an exhaustive list)

Thalassaemias	
Bone	Marrow hyperplasia and bony enlargement
	Reduced bone density
Arthropathy	Joint effusions
	OA and osteoarthropathy
	Deferiprone-associated arthropathy
Other unrelated rheumatic conditions	Inflammatory arthritis (including RA)
	CTDs, including SLE (in particular in patients of African-Caribbean ancestry)
Sickle cell anaemia	
Bone	Vaso-occlusive disease
	Acute painful episodes (sickle cell crisis)
	Avascular necrosis (osteonecrosis)
	Osteomyelitis
	Marrow hyperplasia and bony enlargement
	Reduced bone density
	Growth reduction
Arthropathy	Gout
	OA and osteoarthropathy
	Joint effusions
	Ankylosis
Soft tissue and muscle	Vaso-occlusive disease of soft tissues
	Myoedema, myonecrosis and myofibrosis (with contracture formation)
	Sterile muscle fluid collection
Other unrelated rheumatic diseases	Inflammatory arthritis (including RA)
	CTDs, including SLE (in particular in patients of African-Caribbean ancestry)

Fig. 1 Extensive bone marrow infarcts and severe degenerative joint disease in sickle cell anaemia



(**A**) Radiograph of both knees (weight-bearing views), demonstrating severe loss of joint space involving the tibofemoral compartments. (**B** and **C**) Sagittal T1 (**C**) and sagittal fluid-sensitive (**B**) images demonstrating extensive infarction involving the proximal tibia and background degenerative change at the knee joint, with loss of normal marrow signal of the distal femur (**C**).

improvement in the frequency of episodes with the treatment of her underlying endocrine disease.

Laboratory investigations commonly reveal an acute phase response (including an elevated neutrophil count and/or elevation in CRP). The ESR is not reliable in patients with SCA because there is a failure of the sickled red blood cells to form rouleaux. Clinicians should maintain a low threshold to prescribe antibiotic therapy if there is any concern about infection (according to local microbiological policy). Plain radiographs of the affected region are usually normal in the acute setting, unless for example there is a pre-existing SCA-related MSK complication.

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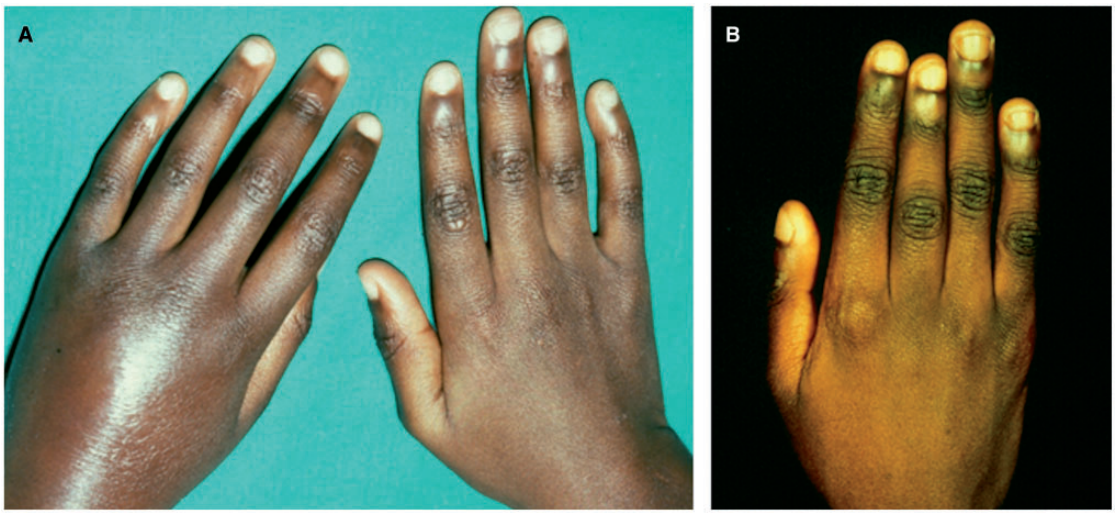
Fig. 2 Dactylitis



(**A**) Dactylitis of the digits and swelling of the carpal bones of the hands. (**B**) Shortened middle digit secondary to previous dactylitis. Photographs from archives of King's College Hospital NHS Foundation Trust.

Later non-specific changes include intermedullary lucency with subsequent sclerosis and periosteal reaction (new bone formation) if the cortex is involved; however, these changes are also seen in osteomyelitis [9, 12]. Imaging techniques that have been investigated to distinguish acute vaso-occlusive disease from osteomyelitis will be considered in the section on osteomyelitis.

Management is largely symptomatic. Patients should be kept warm and well hydrated, with the administration of intravenous fluid only if the patient is unable to take sufficient oral fluid (e.g. owing to vomiting). NSAIDs are often sufficient to control pain; however, some patients may require parenteral opioid-based analgesia, which requires hospitalization. Disch *et al.* [13] report successfully using iloprost to treat a vaso-occlusive episode in a patient with SCA, although this may represent the natural history of gradual improvement of the episode.

Steroid-induced vaso-occlusive disease

Of great concern to rheumatologists, there are a number of case reports and studies that have reported the precipitation of painful vaso-occlusive episodes in patients with SCA who have received steroid therapy, including oral, intraarticular, intramuscular and intravascular administration [14–17].

The onset of the vaso-occlusive episode is often rapid (within a few hours) and can be very severe (including cerebrovascular disease). In a prospective study examining the tolerability of steroid therapy (for systemic and autoimmune disease) in children with SCA over 2 months of treatment, there was a 2-fold increase in frequency of vaso-occlusive episodes, and also an increase in other severe (and potentially life-threatening) complications (e.g. acute chest crisis and stroke) [17]. Therefore, in patients with SCA and inflammatory rheumatic conditions, the therapeutic rationale for initiating steroid therapy (by any route) needs to be considered carefully against the significant potential risk of harm, with judicious use of disease-modifying agents.

Infection

Patients (in particular, children) with SCA are at increased risk of infection because of functional hyposplenism and with a propensity towards encapsulated organisms. Rheumatologists must strongly consider infective MSK complications because they can mimic other SCA MSK complications, such as painful vaso-occlusive disease, and a delay in diagnosis and treatment may result in a poor clinical outcome. Skin infection (in particular, malleolar ulcers) is common in patients with SCA [18, 19] and could potentiality act as a source of deeper bony infection.

Osteomyelitis

Approximately 10% of patients with SCA will develop osteomyelitis during the course of their life, often affecting children and young adults, and can occur in association with septic arthritis [20–22]. Established osteonecrosis is a risk factor for the development of osteomyelitis [23]. The clinical presentation of osteomyelitis is often difficult to distinguish from that of painful vaso-occlusion of bone (although the latter is by far more common), and investigations are commonly non-specific to either condition. Patients present with severe pain and swelling of the affected bone and with tenderness to palpation, often accompanied by pyrexia. If the pyrexia is marked, this might be more suggestive of an infective process.

Blood investigations may reveal evidence of an acute phase response, and peripheral blood cultures may be

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positive in ~50% of patients with osteomyelitis. Although bone biopsy and culture is the gold standard for the diagnosis of osteomyelitis, few patients undergo this. If there is any concern about mycobacterial (*M. tuberculosis*) infection, clinicians should liaise directly with the receiving laboratory to ensure that bone samples are transported in appropriate medium and processed accordingly.

Various imaging modalities have been examined in patients with SCA and osteomyelitis, in particular to distinguish it from vaso-occlusive disease, including US [24–27], MRI (including contrast enhanced) [28, 29], PET [30] and nuclear medicine-based scans (isotope bone and labelled white cell scans) [31, 32]. Common to many of these techniques is that the features of osteomyelitis are non-specific and can also be found in vaso-occlusive disease.

Plain radiographs of the affected area are often normal, although similar to vaso-occlusive disease; changes may be seen only after 1–2 weeks [9]. MRI findings may include low (T1) and high (T2) signal intensity fluid areas. Of note, haematopoietic marrow has a similar appearance on MRI (T1 sequence), and marrow enhancement post-gadolinium can be also be found with avascular necrosis [9, 12]. Many clinicians consider US a useful tool in the assessment of patients with suspected osteomyelitis because it is widely available, quick to perform and non-invasive (which is particularly useful with children). US findings in osteomyelitis may include fluid collection, periosteal reaction and soft tissue changes [12]. In addition, associated joint effusion can be targeted for diagnostic aspiration under US guidance. It is outside of the scope of this review to discuss the specifics of the nuclear medicine imaging techniques; however, these require specialist review and, of note, diffuse marrow involvement in haemoglobinopathies can make the interpretation of labelled white cell scans difficult [9].

Treatment of osteomyelitis is in general the same as for patients without SCA, with typically 6 weeks of appropriate antibiotic therapy based on antimicrobial sensitivities where available. As above, surgical intervention may be indicated if osteomyelitis is associated with large fluid collections and also in those patients with progressive or refractory disease. Some patients may go on to develop chronic osteomyelitis with need for recurrent antibiotic treatment and/or surgery.

Septic arthritis

Septic arthritis is much less common than osteomyelitis in patients with SCA and again may arise as a complication of vaso-occlusive disease and bone infarction [12]. The hip is the most common site of septic arthritis in patients with SCA [22, 23]. Treatment of septic arthritis is in general similar to patients without SCA, with antibiotic therapy usually for a duration of 6 weeks. Early diagnosis is key, and synovial fluid aspiration is mandatory in patients with SCA presenting with the acute swollen joint where infection is suspected.

Disorders of bone

As the primary site of disease in haemoglobinopathies, bone is invariably affected in both patients with SCA and those with thalassaemia. Vaso-occlusive disease and osteomyelitis have been discussed already.

Intramedullary marrow hyperplasia

Although red (haematopoietic) marrow is found throughout the fetal skeleton, in healthy adults it is found only in the axial and appendicular skeleton (the spine, ribs, sternum, pelvis and proximal long bones), with yellow marrow accounting for the rest of the skeleton [9, 12]. In SCA and thalassaemia, there is persistence of red marrow throughout the axial and appendicular skeleton to maintain haematopoiesis because of the increased demand from anaemia [1, 9, 12]. In thalassaemia, bone marrow hypertrophy results in expansion of the bone medullary cavity with thinning of the cortical wall [1, 9]. Common examples of abnormal intramedullary haematopoiesis include the skull (with severe frontal bossing) in β-thalassaemia and the vertebral bodies (with a characteristic fish-mouth appearance due to softening of the vertebral end plates and compression from adjacent intervertebral discs) in SCA [12].

Avascular necrosis (osteonecrosis)

Any bone may be subject to avascular necrosis (often bilateral and multiple sites) in SCA. Most commonly affected are the femoral and also humeral heads; other sites include the vertebrae, pelvis, the small joints of the hands and feet and the mandibular condyles [1, 18, 20, 33, 34].

In a prospective study, which included 2590 patients with SCA, the incidence of osteonecrosis (including detection by at least yearly radiographs) was 2–4.5 cases/100-patient years, with an overall prevalence of ~10% [35]. Reported risk factors for the development of avascular necrosis (of the femoral head) include patients with both SCA and α-thalassaemia, higher haemoglobin and haematocrit, higher frequency of both painful attacks and episodes of hospitalization, history of leg ulcer and osteonecrosis of the humeral head [34–36].

Although many patients with avascular necrosis are asymptomatic, some patients run a chronic disease course with progressive pain and restriction of movement (temporally different from the presentation of acute vaso-occlusive crises) [1, 20]. The natural history of osteonecrosis (irrespective of symptoms) of the femoral head is of progressive collapse requiring arthroplasty, which is often indicated for intractable pain [37, 38]. A Cochrane review concluded that the addition of hip core decompression to physical therapies alone did not confer any additional benefit; however, the authors highlighted that the analysis was based upon only one study and there was high rate of patient attrition [39].

Reduced bone density

The pathophysiology of the development of osteopenia and osteoporosis in both SCA and thalassaemia is complex and often multifactorial. It is a particular feature of thalassaemia intermedia and major. Bone marrow expansion reduces the volume of the cortical wall,

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endocrinopathy may develop from iron overload with abnormalities in sex hormones (including delayed menarche), and vitamin D deficiency is common (particularly in patients from non-temperate areas) [1].

The majority of adult patients with SCA and β-thalassaemia have evidence of reduced BMD, often with established osteoporosis [40–43] with a predilection for the lumbar spine in SCA [43], and with low BMD often already present in young adults (in SCA) [43, 44]. There are a limited number of studies examining risk factors for reduced BMD, and the results of these are in general conflicting, although low BMI has been more consistently associated with SCA and thalassaemia [40, 43]. Low vitamin D status (in particular, deficiency) may have a significant role in patients with SCA but not thalassaemia [44–46]. Males are also more often affected than females in thalassaemia, possibly owing to more severe hypogonadism in males [41, 42, 47].

Patients with haemoglobinopathies should be counselled about their bone health and encouraged to take regular exercise. Children with thalassaemia major should undergo regular BMD assessment from ∼10 years of age [1]. Vitamin D status should be assessed and supplementation offered (if required) to maintain it within the normal range. Regular blood transfusions (to reduce marrow expansion) should be undertaken, with iron chelation (after ∼10 transfusions) to prevent the development of endocrinopathy. Bone active (e.g. bisphosphonate) therapy should be considered in patients with established osteoporosis. In a systematic review that included five randomized controlled trials, adult patients with thalassaemia-associated osteoporosis treated with alendronate, neridronate or zoledronate bisphosphonates experienced a significant improvement in BMD when compared with placebo [48].

Growth

Restriction in growth is recognized in SCA and is likely to be multifactorial in origin, including bone marrow hyperplasia, epiphyseal compromise (from infarction), endocrine abnormalities (e.g. hypogonadism) and the effect of the chronic disease process, including delayed puberty and premature closure of the growth plates [1, 49–51].

Arthropathy

Inflammatory arthritis

The coexistence of inflammatory arthritis and haemoglobinopathies has been reported rarely in the literature. Local phagocytosis of sickled red cells may drive the development of inflammatory arthritis in SCA [52, 53].

In a small number of case reports and series, patients with SCA have developed either RA or JIA (often seropositive), with a severe resultant destructive arthropathy [15, 54–56]. The severe arthropathy observed may be the result of the additive effect of RA on a background of SCA MSK disease [15, 55]. In addition, there is often a marked delay in diagnosis that may be due to both the frequency of MSK symptoms in SCA and the rarity of RA in individuals with an African-Caribbean ancestry [55]. MSK imaging (in particular, MRI) may help to establish the presence of an inflammatory arthritis on a background of established SCA MSK disease, where diagnostic uncertainty may exist, and which could have significant therapeutic implications (e.g. necessitating the introduction and/or increase of immunosuppressive therapy) [15, 56]. The inflammatory arthritis (again, often seropositive) described in patients with β-thalassaemia major is likely to be due to the coexistence of RA; patients often run a mild clinical course, with a low reported frequency of extra-articular manifestations [57, 58].

Of interest, an association between β-thalassaemia and a number of rheumatic and non-rheumatic autoimmune conditions has been reported in the literature. It has been postulated that the β-globulin locus may reside in close proximity to key autoimmunity genes, or that the reduced expression of haemorphins (endogenous opioids with anti-inflammatory actions) in patients with thalassaemia may drive the development of systemic autoimmune disease [59].

Patients with haemoglobinopathies and inflammatory arthritis should be treated along standard lines. As above, steroid therapy should be used with extreme caution and in liaison with haematology, because this may potentially trigger serious vaso-occlusive complications. Disease-modifying therapy requires meticulous monitoring because there may be severe haematological adverse effects from many of these agents (e.g. bone marrow suppression from many agents and haemolytic anaemia secondary to SSZ). Anti-TNF agents have been used successfully in patients with haemoglobinopathies, and several authors have postulated that anti-TNF blockade may be of particular benefit in patients with SCA because of increased synovial TNF-α, including that from local sickling of red blood cells [15, 55].

Gout

The occurrence of gout is uncommon in patients with SCA and rare in thalassaemia [60–65]. Serum uric acid is often elevated in patients with SCA as a result of both the overproduction of purines from ineffective erythropoiesis and the reduced renal clearance of urate because of reduced renal function [61, 62]. Gupta *et al*. [65] concluded in their retrospective study that elevated serum uric acid, poor renal function and low haemoglobin are risk factors for patients with SCA to develop gout. The majority of patients had a monoarticular presentation, with a relatively young age of onset (around the fourth decade) and predominance for males [65]. Patients in general often respond well to standard therapy for gout (e.g. colchicine and urate-lowering therapy), and anakinra has been reported to be effective in refractory disease [65]. Again, steroid therapy has been associated with the provocation of painful vaso-occlusive crisis in patients with SCA and gout [65].

Joint effusions

Joint effusions may occur in patients with haemoglobinopathies (in particular, SCA) [25, 66]. Joint effusions are often non-inflammatory; however, inflammatory effusions

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may develop where the articular surface has been subject to vaso-occlusion. Again, it has been postulated that the local phagocytosis of sickled cells may drive the development of inflammatory effusions in SCA [52, 53]. In patients with β-thalassaemia, joint effusions may occur in relation to deferiprone-related arthropathy (also called L1, an oral iron chelator used to prevent cardiac iron overload) [67]. If there is any clinical suspicion of an effusion in association with septic arthritis, then synovial fluid must be aspirated for analysis.

OA and osteoarthropathy

Patients with SCA may develop OA, which may occur as a complication of osteonecrosis if the articular surface is involved. Historically (before the availability of effective chelation therapy), osteoarthropathy (in particular of the ankles) was reported in patients with thalassaemia major with significant iron overload, which was likely to be multifactorial in aetiology, including bone marrow expansion, hypoparathyroidism and the deposition of iron within the joint [1].

Ankylosis

Ankylosis of joints, including but not limited to the knees and temporomandibular joints, has been described in patients with SCA [33, 56, 68]. The aetiology of this is likely to involve extensive infarction of bone (and muscle) around the joint; although, in some patients, an inflammatory rheumatic condition could be considered.

Deferiprone-associated arthropathy

A characteristic non-inflammatory arthropathy has been reported in patients with β-thalassaemia who have received treatment with deferiprone. The resultant arthropathy is often mild and tends to affects the large joints (with a predilection for the knees) [1, 67, 69]. Characteristic MRI abnormalities have been reported to include subchondral bone irregularity, joint effusion and patellar beaks [67]. Specific treatment is usually not required, with gradual spontaneous improvement, and not requiring discontinuation of deferiprone, although patients may benefit from anti-inflammatory agents if not contraindicated [1, 69].

Muscle disease

Soft tissue, in particular muscle vaso-occlusive disease, is often overlooked in patients with SCA. This is probably much more than common than recognized and may occur in parallel with acute bone infarction, which may mask the muscular involvement. Vascular occlusion results in myoedema, which untreated may progress to irreversible myonecrosis, with the later development of established myofibrosis and contractures [70]. Tageja *et al*. [70] reported (including from the medical literature) a series of 13 patients with SCA who developed myonecrosis. They concluded that common characteristics were that patients were often male, young and with a history of previous sickle crises. Patients present with symmetrical proximal muscle weakness and muscle pain, which is often atypical (more severe and different from their previous bony crises) and associated with swelling and induration of the affected musculature [70]. A rare (but very important) differential may therefore include (in selected patients) idiopathic inflammatory myopathies. Of note, the authors comment that few cases have reported the creatinine kinase concentration, although of note, this was normal in three (out of six) patients. Of caution, two patients required fasciotomies for compartment syndrome. Sterile muscle fluid collections have also been described, although it is unclear whether these need to be drained [70]. Again, if there is any clinical suspicion of an infective process complicating muscle involvement (e.g. the development of an abscess), then this should be managed accordingly (e.g. with drainage and appropriate antimicrobial therapy).

CTD

Although high titres of autoantibodies, including ANA, have been described in patients with SCA, the coexistence with an autoimmune CTD is relatively uncommon. However, SCA and SLE are more common in those individuals of African-Caribbean ancestry. In one prospective study, which included 88 patients with SCA, around half of the patients ($n = 43$) had a positive ANA, including a strongly positive result (defined as a titre of $\geqslant 1{:}50$ and $1 \geqslant 200$, respectively) [71]. Over a follow-up period of 6 years, no patients developed a CTD (and only one developed RA). Based upon the limited literature base, CTDs in patients with SCA often tend to run a milder clinical course than in unaffected individuals [72, 73].

Conclusion

In conclusion, MSK complications are common in patients with haemoglobinopathies. Rheumatologists should consider other causes of MSK symptoms (e.g. inflammatory arthritis and CTDs) in patients with haemoglobinopathies. In patients with SCA, it is often clinically challenging to distinguish between vaso-occlusive disease and osteomyelitis. Treatment with steroid therapy in patients with SCA is potentially hazardous, with possible life-threatening complications, even with intra-articular administration. There is a limited evidence base to guide the management of many of the MSK complications in patients with haemoglobinopathies, and future high-quality research is a priority to bridge this deficit. Patients with haemoglobinopathies and rheumatological conditions should be managed by a dedicated multidisciplinary team (in particular, with colleagues from haematology) to ensure that they receive the optimal treatment of their often-multifactorial MSK complications.

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