INHERITED DISORDERS

The arthropathy of haemochromatosis and the role of the orthopaedic surgeon

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KEYWORDS
Haemochromatosis; Arthropathy

Summary
Haemochromatosis is thought to be an uncommon condition which may present as a disabling symmetrical polyarthropathy. Early diagnosis can prolong life by preventing the development of co-morbidities.

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Introduction
Haemochromatosis was first described in 1865 by Tousseau in a diabetic patient with the characteristic bronzed skin pigmentation and the stigmata of liver cirrhosis. It is characterised by abnormal deposition of iron in tissue parenchyma throughout the body. Despite affecting 1 in 250 people within Northern Europe, haemochromatosis is still erroneously considered to be a rare condition. It can be divided into two broad categories: primary which predominantly occurs in the Caucasian population and is caused by a genetic mutation and secondary to a haematological disorder such as sideroblastic anaemia, myelofibrosis, excess blood transfusion therapy and porphyria cutanea tarda.

Schumacher first described an associated arthropathy in 1964. This had been regarded as a rheumatological problem for a number of years, but the need for orthopaedic intervention was identified. This article describes the typical features of the arthropathy and the management of primary haemochromatosis.

Iron homeostasis—physiology

Approximately, 20mg/day of iron is needed by the bone marrow to maintain erythrocyte production. The main source is from the destruction of mature erythrocytes and it is transported to the marrow by binding to plasma transferrin. Up to 2mg/day of iron is ingested and transferred to the plasma component or stored as ferritin in the liver. This iron store is only depleted when erythrocytes come to the end of their life span. This slow consumption of iron stores is the reason that excess iron in the body may easily accumulate (Fig. 1).

Iron homeostasis—pathophysiology

Iron only causes tissue damage when supply exceeds demand. The mechanism of tissue injury leading to arthropathy is unclear, but there have been many proposed theories including stimulation of collagen production by excess iron, and lipid peroxidation of organelles. There may be even be an inflammatory component as in one study, finely granular iron deposition was seen in macrophages located within synovium. The end result of tissue injury is the deposition of iron within organ parenchyma.
Genetics

Primary haemochromatosis is an autosomal recessive condition due to different mutations in the HFE gene on chromosome 6: C282Y (tyrosine is substituted for cysteine at amino acid position 282) and H63D (aspartic acid is substituted for histidine in position 63). The more significant is C282Y which leads to an increased absorption of iron from the gut resulting in progressive iron overload in parenchymal organs such as the joints, liver, pancreas, pituitary gland, heart and skin. The lesser mutation, H63D, also leads to an increase in iron absorption but is not as destructive. Although the genetic defect is present at birth, it rarely manifests until late adulthood, and even then predominantly in homozygotes. Men are nine times more at risk than women, probably due to the protective effect of menstrual loss of iron.

Histopathology of arthropathy

Sheldon was the first to note that haemosiderin deposits were present in the articular cartilage and synovium of patients with haemochromatosis. Initially the underlying biochemical pathology was not understood, but it is now clear that the chronic excess of unbound circulating iron has a toxic effect on chondrocytes. This leads to the characteristic features of the arthropathy, narrowing of the zone of calcified cartilage, splitting and avulsion of articular cartilage at the level of the tidemark (Fig. 2), calcium pyrophosphate deposition and eventually osteonecrosis.

Clinical features

When haemochromatosis was first described, the typical clinical features included the triad of cirrhosis, diabetes mellitus and hyperpigmentation of the skin. The distinctive hyperpigmentation of haemochromatosis is a result of iron deposition in the skin causing an increased production of melanocytes. This brown, bronze or slate grey appearance tends to be most prominent on sun-exposed skin, particularly on the face. Due to earlier diagnosis, only 8% of patients display the distinctive triad on presentation. The most common presentation (84%) is with features of chronic liver disorder. Thus, a typical patient may present with abdominal pain and moderate hepatomegaly. Joint pain is the next most frequent presenting complaint (11% of patients) (Table 1). Those diagnosed late are more likely to present with diabetes (due to destruction of the endocrine pancreas), a multitude of cardiac presentations due to iron deposition in the Bundles of His and Purkinje fibres such as congestive cardiomyopathy, conduction defects and arrhythmias or hepatocellular carcinoma. Other endocrine effects include decreased gonadotrophin production and resultant secondary infertility due to pituitary impairment, which can lead to diffuse osteoporosis.

Arthropathy

Arthropathy associated with primary haemochromatosis occurs in approximately 50% of patients. The symptoms are usually chronic, but the arthropathy may present acutely with a hot, swollen joint that can mimic gout or acute rheumatoid arthritis. In up to 72% of cases of acute joint symptoms, there may be radiographic features of chondrocalcinosis with calcium pyrophosphate crystals in aspirated joint fluid accounting for this presentation and thus, refuting the diagnosis of gout.

The arthropathy is usually non-inflammatory and degenerative, affecting the small joints (hands) first and the larger joints (hips, knees, ankles) years later. The characteristic presentation is of a symmetrical polyarthritis, which may lead to the erroneous diagnosis of rheumatoid disease. However, the characteristics of rheumatoid disease such as synovial thickening, ulnar deviation of the fingers and rheumatoid nodules are not present, and the rheumatoid factor test is negative and a synovial biopsy usually does not show inflammatory changes.
Classically the arthropathy of haemochromatosis causes a decreased range of motion at the index and middle metacarpophalangeal joints (Fig. 3). In a study of 31 patients with haemochromatosis, 30 patients showed this distribution of arthropathy. Nine patients also displayed a comprehensive arthropathy affecting the larger joints. In many cases, joint pain may be the only noticeable symptom suggestive of the disorder. Sixteen out of 25 patients in another study had reported symptoms of arthralgia up to 3 years before haemochromatosis was diagnosed.

Investigations

A comprehensive haematincs profile may suggest the diagnosis of haemochromatosis. In primary haemochromatosis, the serum iron concentration is usually greater than 150 mcg/dl. The transferrin saturation test can detect how much iron is bound to transferrin and total iron binding capacity measures how well iron is transported around the body. Serum ferritin levels can indicate the amount of iron in the liver. Liver function tests may confirm chronic liver disease and in times past, in conjunction with increased liver density on CT, would have led to a liver biopsy to look for excess stainable iron.

However, the discovery of the HFE mutation has altered the way the condition is diagnosed. Genetic tests for the C282Y and H63D mutations can confirm the diagnosis and identify asymptomatic patients.

Radiographic features

In general, the arthropathy follows a degenerative rather than inflammatory pattern and the radiographic features are similar to osteoarthrosis, i.e. joint space narrowing, subarticular cyst formation, sclerosis and osteophyte formation. In contrast to osteoarthrosis, these changes follow a symmetrical pattern. Moreover, chondrocalcinosis is known to affect up to two-thirds of patients with haemochromatosis-associated arthropathy and there may be radiographic features of this inflammatory process in menisci of the knee, the triangular fibrocartilaginous complex, intervertebral discs of the lumbar spine and in the symphysis pubis.

Involvement of the index and middle metacarpal heads is characteristic. Early features in the hand include subarticular cysts in the metacarpal head surrounded by a sclerotic border. These cysts can progress and extend into the joint space causing narrowing of the joint space and claw osteophyte formation (Fig. 3). In addition, there may be enlargement of the metacarpal heads and the proximal carpal row and the distal radio-ulnar joint may also be affected with cyst formation. In the foot and ankle, radiograph changes degenerative joint disease of the ankle, naviculocuneiform and metatarsophalangeal joints.

Larger joints such as the shoulder and elbow are less frequently affected, and they typically demonstrate less dramatic sclerosis and cyst formation. In the hip, a wedge-shaped subchondral radiolucency deep to the articular surface of the femoral head is thought to be pathognomonic.

<table>
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<th>Table 1 Clinical features of haemochromatosis.</th>
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<td>Symptoms and signs of haemochromatosis</td>
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<td>Symptoms (frequency %)</td>
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<tr>
<td>Abdominal pain (16%)</td>
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<td>Joint pain (11%)</td>
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<td>Weakness (9%)</td>
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<td>Symptoms of diabetes (2%)</td>
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<td>Frequent infections</td>
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<td>Loss of libido</td>
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<td>Breathlessness on exertion</td>
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<td>Increased skin pigmentation</td>
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<td>Loss of body hair</td>
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<td>Menstrual irregularity</td>
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Figure 3 Plain radiographs demonstrating joint space narrowing and claw osteophyte formation typical of the arthropathy of haemochromatosis involving the index and middle metacarpophalangeal joints.
of primary haemochromatosis.\textsuperscript{11} Another prominent feature in the hip was the dense calcification of the fibrocartilage of the articular labrum\textsuperscript{7} (Fig. 4).

**Practice points**

- Affects 1 in 250 Northern Europeans
- Predominantly male
- Presents in middle age
- Index and middle MCPJ commonly affected
- Symmetrical polyarthritis

**Medical management**

Venesection continues to be the mainstay of treatment. A unit of blood of 450 ml contains 220 mg of iron. Blood is taken weekly until ferritin concentration is less than 20 mcg/l and the target transferrin saturation level is below 50\%. This may take years to achieve. Once achieved, maintenance therapy of venesection every 4 months is needed to maintain normal levels. At this stage, patients may then have a normal life expectancy provided that they have not developed other chronic complications such as diabetes, cirrhosis or cardiac involvement.\textsuperscript{12} Interestingly, venesection does not appear to affect the symptoms of arthralgia and these symptoms may even manifest after therapy has been commenced.\textsuperscript{8,13}

**Orthopaedic management**

Aside from the holistic approach to patient management and establishing the diagnosis of haemochromatosis, the orthopaedic management of diseased joints is poorly documented,\textsuperscript{4,6,10,13-15} but seems to reflect current practice for the surgical management of other arthropathies. The key difference lies in the age and activity levels of the patient population that suffer from haemochromatosis. They are predominantly male, in the fourth or fifth decade of life exhibiting a bilateral, symmetrical joint disease, which has implications when considering primary arthroplasty surgery especially with symmetrical joint involvement. As the early diagnosis of haemochromatosis leads to a normal lifespan, patients require revision arthroplasty surgery.

Such literature as there is tends to focus on total hip arthroplasty (THA). One paper reported that 10 out of the 28 patients with an average age of 60.6 years required THA.\textsuperscript{16} In a series of five patients with hip arthropathy of haemochromatosis, three of these patients went on to THA.\textsuperscript{15} The success of these arthroplasties is unclear.

There is only one series looking at the outcome of THA for haemochromatosis.\textsuperscript{4} Over a 10-year period, 19 total hip

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**Figure 4** Plain AP pelvic and lateral hip radiographs demonstrating the arthropathy and how the appearances could be mistaken for early rheumatoid disease.

**Figure 5** Plain radiographs demonstrating the ankle arthropathy.
arthroplasties were performed on 15 patients with hip arthropathy. The average patient age was 59 years. Patients were assessed using the Hospital for Special Surgery hip score (maximum score 40 points). Patients experienced an average improvement in function from 15 to 30 points after surgery. One patient had to undergo a revision due to acetabular loosening; the focus of a more recent study. Lunn et al.\textsuperscript{17} compared a group of primary THA with a group of revision hip arthroplasties and found that patients who are homozygous for the C282Y mutation of the HFE gene appear to have an increased risk of developing aseptic loosening.

Total knee arthroplasty (TKA) for haemochromatosis arthropathy has not been specifically studied. Two papers reviewed TKA with a variety of prostheses and fixation techniques in patients under the age of 50 years\textsuperscript{14,18} including small numbers with haemochromatosis (2–10%). No comment was made as to whether the disease process was associated with poor results or early failure.

Similarly, the management of haemochromatosis ankle arthropathy has been briefly discussed in the literature. Conventional wisdom has very narrow indications for total ankle arthroplasty (TAA) especially in younger, more active patients, and generally, foot and ankle surgeons try and avoid bilateral ankle fusions, particularly if there are degenerative changes within the midfoot. Two papers address TAA for this condition. Hintermann performed TAA on two patients with haemochromatosis out of a total of 48 patients\textsuperscript{19} and while the results were good, no specific mention was made of the two cases. Another paper specifically addressed TAA in haemochromatosis. Four male patients (average age 60 years) underwent five total ankle arthroplasties.\textsuperscript{2} All patients had bilateral, symmetrical ankle arthropathy with radiographic uniform loss of tibiotalar joint space with other degenerative changes (Fig. 4).

Interestingly, three of the four patients in this latter series had undergone other large joint arthroplasties: hip, knee and elbow (Figs. 5 and 6).

There is even less in the literature regarding the upper limb. While involvement of the shoulder, elbow and wrist, is well documented, the orthopaedic management is not clear. There is a case report using Swanson’s arthroplasty for metacarpophalangeal joint arthropathy.\textsuperscript{13}

**Discussion**

Haemochromatosis has long been considered a general medical condition. While this remains true, not infrequently, it may present as an arthropathy. Given that early diagnosis of the condition leads to an improved patient prognosis, any middle-aged patient with a symmetrical arthropathy should be investigated for haemochromatosis by the orthopaedic surgeon. There is a range of surgical options available for managing diseased joints including arthroplasty, although some evidence may show that the disease predisposition to aseptic loosening.\textsuperscript{17} Therefore, it is clear that further research and audit of the outcome of surgery for this arthropathy is essential.

**References**


![Figure 6](https://example.com/fig6.png) The radiographic appearances of the arthropathy of haemochromatosis affecting the elbow.


