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Haemochromatosis arthropathy – a conundrum of the Celtic curse

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Abstract

Genetic haemochromatosis is an autosomal recessive disorder, mostly due to HFE gene mutation, leading to loss of hepcidin and unregulated iron loading. The consequences include hepatic fibrosis, cardiomyopathy and skin pigmentation, and these sequelae along with fatigue may be prevented by 'de-ironing'. Joint pain is frequently reported at diagnosis and an arthropathy that is essentially accelerated osteoarthritis may develop, with onset at a younger than expected age, involvement of typical and atypical joints, such as metacarpophalangeal and ankle, exuberant osteophytes and rapid progression to cartilage loss and the need for arthroplasty. The arthropathy differs from the other features in not responding to de-ironing, new joints becoming affected once patients are in maintenance, and, intriguingly, classic cases occur in the absence of iron overload with major and minor HFE mutations. These anomalies present a conundrum that raise the question whether HFE mutations have an arthritogenic consequence independent of hepcidin and iron.

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Genotype, phenotype, detection and response to 'de-ironing'

Genetic haemochromatosis (GH) is an autosomal recessive disorder in which intestinal iron hyperabsorption leads to tissue iron deposition and organ dysfunction.[1,2] In Northern European populations mutations of the HFE gene on chromosome 6 are responsible for the majority of cases of GH, with substitution of tyrosine (Y) for cysteine (C) at position 282 or aspartic acid (D) for histidine (H) at position 63 of the HFE protein being the most frequent abnormalities. The gene frequencies are common (Table 1). Penetrance to the clinical phenotype of iron overload is much lower, almost exclusively restricted to the C282Y homozygous mutation, and only occurring in approximately 10–30% with this genotype, with one estimate to be <1%[3] and others reporting 29% of men over the age of 40 years and 11% of post-menopausal women.[4,5] The mechanism of iron loading is a consequence of a reduction in the hormone hepcidin, which degrades ferroportin, the sole mechanism for iron release from iron-exporting cells, such as the duodenal enterocyte, hepatocyte and macrophages.[2] As a consequence, iron release from the gut and from internal recycling is unchecked. In Asian populations GH is also seen, but usually as a consequence of mutations in the haemojuvelin gene on chromosome 1, which also results in hepcidin deficiency.

Iron overload leads to a wide variety of organ and tissue sequelae, characteristically described by the triad of hepatic fibrosis, diabetes and skin pigmentation leading to the term 'bronzed diabetes'. Other critical organ features include cardiomyopathy, hypopituitarism and hepatocellular carcinoma, with dysfunction being a direct consequence of the amount of iron deposition. In contrast, and by no means less intrusive, the most frequently reported symptoms at diagnosis are fatigue and joint pain, often predating diagnosis by 5 years or more.[6,7] Iron depletion by venesection, termed 'de-ironing', is effective if commenced early, avoiding or preventing progression of many of these manifestations, such as hepatic and cardiac disease, and reversing others, such as hepatic fibrosis and fatigue.[8,9] A pre-venesection serum ferritin <1,000 μg/l is taken to be a marker of good prognosis,[5,10] and ideally all cases should be detected and commenced on a venesection programme before this threshold is exceeded. Where there is a family history of the condition regular measurement of transferrin saturation and ferritin will lead to an early diagnosis. For other patients detection of iron overload may be serendipitous, for example as a consequence of random testing or part of a non-specific well person health screen. However, for >50% of patients recognition of symptoms and signs is required to prompt measurement of iron indices and then gene analysis.[7] Unfortunately, most of the features of iron overload are insufficiently characteristic to prompt early suspicion, and many years often pass before the diagnosis is considered and investigations initiated.

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Genotype	Prevalence
H63D/WT (HDCC)	1 in 8
C282Y/WT (HHCY)	1 in 12–15
C282Y/H63D (HDCY)	1 in 40
H63D/H63D (DDCC)	1 in 42
C282Y/C282Y (HHYY)	1 in 250–300

Table 1 Gene frequency of HFE mutations in people of Northern European ancestry

C282Y: HFE gene mutation resulting in amino acid substitution of tyrosine (Y) for cysteine (C) at amino acid position 282 in the HFE protein; H63D: HFE gene mutation resulting in amino acid substitution of aspartic acid (D) for histidine (H) at amino acid position 63 in the HFE protein; WT: HFE gene wild type

Haemochromatosis arthropathy, overview

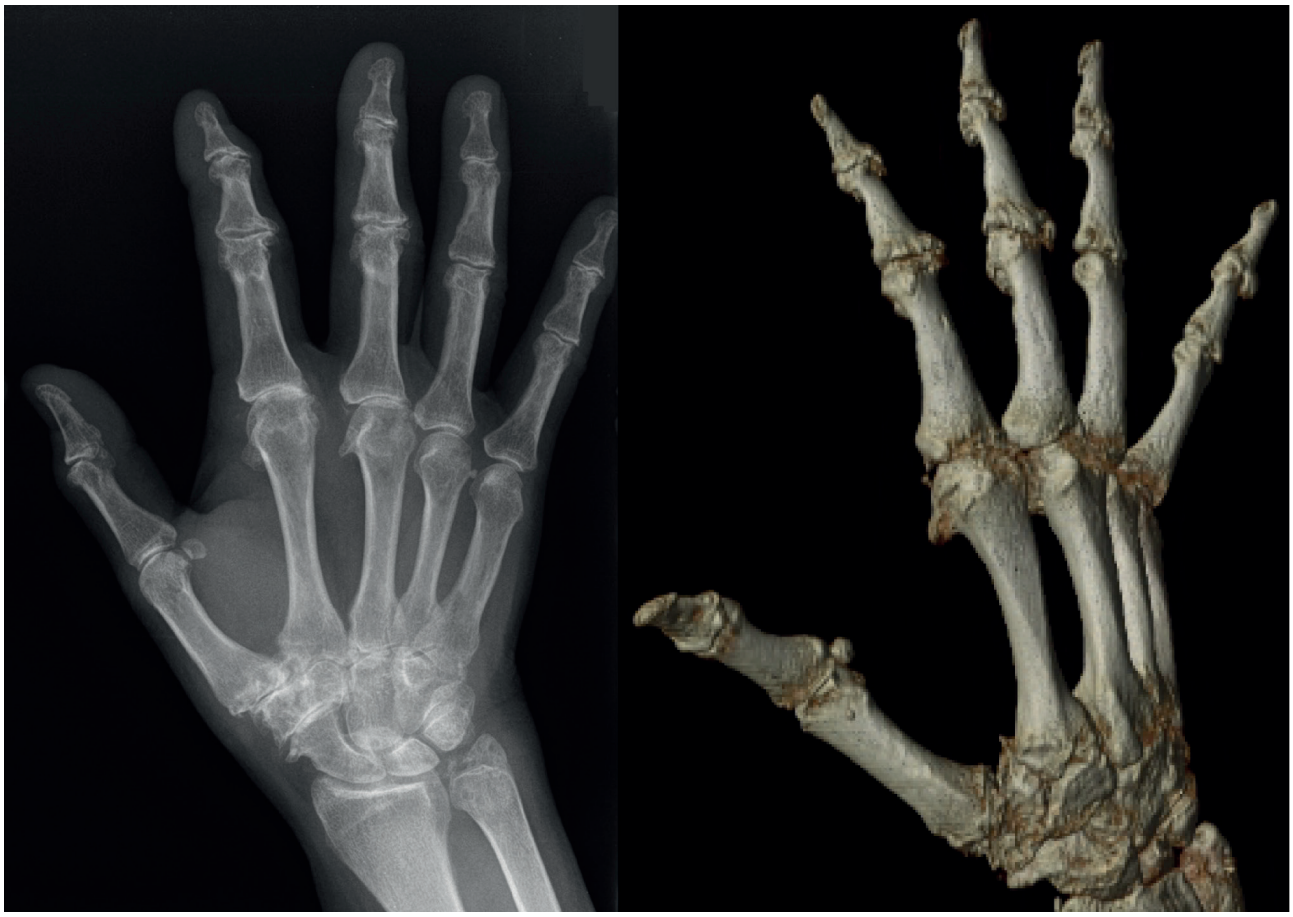
From an early stage the majority of GH patients report joint symptoms,[6,10] for example at diagnosis in 77% of a group of 62 GH patients attending a specialist haemochromatosis arthropathy clinic and in 76% of 470 GH respondents to a questionnaire.[7] Arthropathy has been reported to be significantly associated with a high ferritin at presentation with a similar threshold of peak ferritin >1,000 μg/l conferring increased risk.[5,10–13] Whilst there are no classification criteria for the arthropathy of haemochromatosis, the features are well described. Superficially patients have the clinical and radiographic characteristics of osteoarthritis (OA),[6,7,10,14,15] including chondrocalcinosis visible on plain radiographs in up to 50% of cases.[14] The characteristics that distinguish it from primary generalised OA are summarised in Table 2. In broad terms GH patients have a phenotype of 'accelerated OA' with onset at a younger than expected age in the absence of trauma or deformity and a high rate of joint replacement surgery.[16] Affected joints include those typically affected by OA, such as hip, knee, proximal and distal interphalangeal and first carpometacarpals, and importantly from a diagnostic perspective, frequent involvement of joints not often affected by OA, notably the second and third metacarpophalangeals and ankles.[6,7,17–20] The usual radiographic features of OA are seen, with joint space narrowing, osteophytes and subcortical cysts on plain radiographs, and extensive cysts, bone marrow lesions and full thickness cartilage loss on MRI. The concept of accelerated OA is supported by exuberant osteophytes giving the term 'hooks' in association with the metacarpophalangeal joints and elsewhere, as illustrated by the 3D-reconstructed CT of the hand of a patient with the C282Y homozygous genotype in Figure 1. A comparison with hand OA has shown more severe radiographic changes in GH patients at the metacarpophalangeal and wrist joints but less so in first carpometacarpal, proximal and distal interphalangeal joints.[21] Focussing on the ankle, which is rarely affected by OA in the absence of trauma,[22,23] MRI features in GH patients compared to primary OA controls confirm the concept of accelerated OA with significantly larger and more extensive cysts/bone marrow lesions (Figure 2), osteophytes and full thickness cartilage loss.[24] Histological studies of haemochromatotic joints are restricted to small series or isolated cases.[25,26] In 15 patients with GH, synovial histological features from knee, hip, ankle, wrist and phalangeal samples were very similar to a control group with OA, with the exception of more synovial haemosiderin deposition associated with infiltrating neutrophils and increased sublining layer CD68-positive macrophages.[27]

Table 2 Comparison of the common characteristics of primary generalised osteoarthritis and the accelerated osteoarthritis phenotype of haemochromatosis arthritis

	Primary generalised osteoarthritis	Haemochromatosis arthropathy
Gender prevalence	Female > Male (knee, hand)	Male > Female
Average age of onset	>50 years	40–55 years
Preceding joint injury/deformity	Common (hip, knee)	Unusual
Common affected joints	Hip, knee, first CMC, PIP, DIP	Hip, knee, first CMC, PIP, DIP, MCP 2 and 3, ankle
Osteophytes	Present	Exuberant
Subchondral cysts/bone marrow lesions (MRI)	Present	Larger and more numerous
Progression to arthroplasty	Usually slow	Higher prevalence and can be rapid

CMC: carpometacarpal joint; DIP: distal interphalangeal joint; MCP: metacarpophalangeal joint; PIP: proximal interphalangeal joint

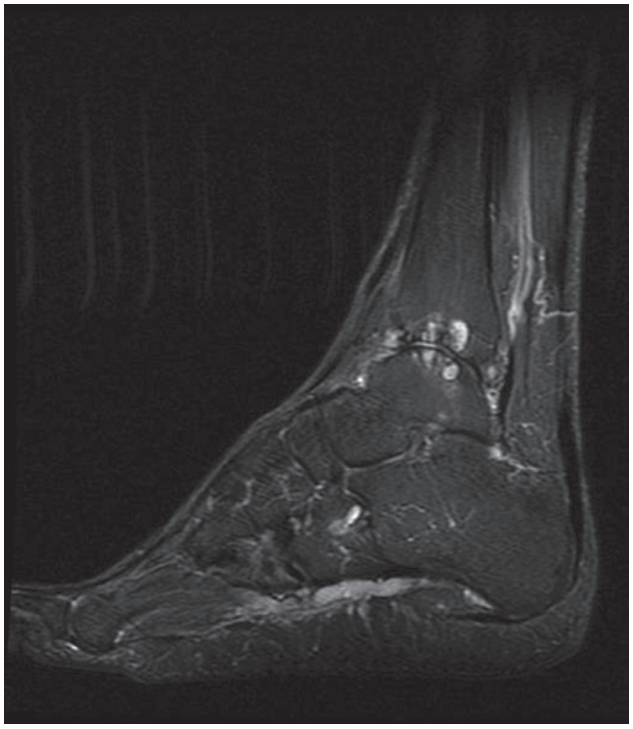
Figure 1 X-ray and 3D-reconstructed CT scan of the right hand of a 61-year-old female with the C282Y homozygous genotype, peak ferritin 1,100 μg/l, showing widespread and florid features of osteoarthritis, including large osteophytes at the second and third metacarpophalangeal joints (hook appearance) and also at scapho-trapezium, first carpometacarpal, proximal and distal interphalangeal joints with joint space narrowing and subchondral cysts



The anomalies of the arthropathy

Thus, the arthropathy of GH is an early manifestation of this condition, with joint pain reported by the majority of affected people. Whilst superficially easily confused with primary generalised OA, the distinguishing features of an accelerated phenotype accompanied by involvement of atypical joints are characteristic. However, unlike other manifestations of GH, the arthropathy of GH distinguishes itself by several intriguing anomalies, which call into question the absolute necessity for iron overload. Firstly, joint pain and stiffness have been reported in most series to only rarely improve following de-ironing,[6,7,28,29] with one exception.[13] This is unlike other features, such as fatigue, bronzed skin colouration and liver fibrosis, which are reported to improve.[8,9] Secondly, after de-ironing new joints are reported to become affected, and chondrocalcinosis seen to progress, whereas unaffected organs are spared from the effects of GH after iron has been removed.[6,7,14,30] This anomaly has been postulated to reflect sequestration of iron in the joint, preventing release into the circulation, and hence making venesection ineffectual.[15,31] There are few histological studies to confirm or refute this assertion; however, iron is not consistently seen in cartilage and synovial biopsies,[26,31,32] and a literature review comparing the arthropathies of haemochromatosis and haemophilia concluded that whilst certainly toxic the presence of iron itself is not the sole element responsible for inducing synovitis in haemochromatosis.[25] A third anomaly is that cases of classic haemochromatosis arthropathy are seen without iron overload in patients with the C282Y homozygous genotype, and also in people with lesser HFE mutations, such as compound C282Y/H63D, heterozygous C282Y, H63D homozygous or H63D heterozygous genotypes.[18,19,33–35] Such reported cases have been revealed by an astute clinician requesting HFE analysis even though transferrin saturation and ferritin were normal, with curiosity driven by pattern recognition of the typical features of this arthropathy. The prevalence of joint disease in non-iron loaded people with HFE mutations is hardly known as HFE screening programmes in the general population are not undertaken, given the low penetrance of even the major C282Y homozygous genotype to iron overload. One study of 176 patients with hand OA found a higher than expected prevalence of the heterozygous C282Y genotype of 12.5% compared to 7.8% in an unselected control population.[36] A random HFE genotype analysis of 2,095 participants aged over 55 years in the Rotterdam population-based cohort study revealed a significantly higher frequency of OA features, such as arthralgia, osteophytes, hand radiograph joint space narrowing and Heberden nodes, in H63D homozygotes and C282Y/H63D compound

Figure 2 Sagittal short-tau inversion-recovery MR image showing tibial plafond and talar dome subchondral lesions consisting mainly of cysts with surrounding ill-defined bone marrow lesions, characteristic of haemochromatosis arthropathy



heterozygotes than in non-carriers.[34] Such population clues and individual case reports confirm the existence of cases of accelerated OA typical of haemochromatosis arthropathy without iron loading, and this, together with the other anomalies, presents a conundrum. On one hand, iron in excess is toxic,[25] and when in excess in C282Y homozygous cases the arthropathy seen is often severe.[10] On the other hand, why do we inconsistently see iron deposition in affected joints, why does 'de-ironing' fail to prevent progression of arthropathy to new joints and how does classic haemochromatosis arthropathy develop in people with HFE mutations and no iron overload? This latter group may be the key to understanding these anomalies. Epidemiologic data showing the prevalence of HFE mutations among large populations of people with OA, and proteomic analyses from their joint tissue would be welcome.

Link between the HFE protein and arthropathy

An understanding of the function of the HFE gene and its protein might lead us to some of these answers. The protein encoded by the HFE gene is a class Ib major histocompatibility molecule associated with β2 microglobulin (β2m). For iron regulation the HFE protein binds to transferrin receptor-1 in competition with iron. Rising transferrin-bound iron displaces HFE protein rendering it available for binding to alternative ligands, such as the cation-independent mannose-6-phosphate receptor[36] and the bone morphogenetic protein (BMP) type 1 receptor, ALK3.[2,37] Binding of the HFE protein to non-transferrin ligands, when displaced by iron, thus provides a mechanism for stimulation of hepcidin production and hence a homeostatic iron-sensing function. The HFE C282Y mutation results in disruption of a disulphide bond causing mis-folding and loss of association of the HFE protein with β2m. This prevents the HFE protein being expressed at the cell surface and it is therefore not available to bind to the transferrin receptor or other non-transferrin ligands, explaining how its stimulatory effect on hepcidin synthesis is impaired or lost.[2,38] That the association with β2m is critical to the iron regulatory function of the HFE protein is demonstrated in β2m knockout mice, which have an iron-overload phenotype.[2] The H63D mutation, which rarely leads to iron overload but is associated with arthropathy, effects the extracellular domain of the HFE protein without impairing its association with β2m or cell surface expression.[38] The mutation is located near the peptide-binding groove, which might, therefore, affect binding to ligands. The H63D-mutated HFE protein does bind to the transferrin receptor, but not as efficiently as the wild-type protein, leading to a potential functional consequence.[39] Similarly, impaired binding to other ligands could provide a mechanism for an arthritogenic consequence, which might be more completely induced by the C282Y mutation where the HFE protein is not expressed on the cell surface.

The HFE protein forms part of a multiprotein complex including BMPs, haemojuvelin and transferrin receptor 2.[2] The intracellular signalling of this complex involves BMP receptors, especially ALK3, and small mothers against decapentaplegic (Smad) signalling. The functions of this pathway may therefore lead us to a non-hepcidin effect, perturbed by absent expression (C282Y) or abnormal receptor binding (H63D) of the HFE protein. Analysis of hepatic expression of BMP/Smad genes in GH patients with iron overload compared to controls reveals impaired BMP signalling and, specifically, upregulation of the inhibitors Smad6 and Smad7.[40] A link to an accelerated osteoarthritis phenotype, if this were found in chondrocytes, is possible given the observation that Smad7 has an important role in skeletal development and chondrocyte maturation.[41] Over expression of Smad7 blocks transforming growth factor-β (TGF-β)-mediated chrondrocyte proliferation and proteoglycan synthesis, both key physiologic functions of cartilage that when lost initiate OA.[42–45] Interleukin 1 (IL-1) is also of interest as this is a key cytokine in crystal-mediated arthropathies, given the association of haemochromatosis arthropathy with calcium pyrophosphate deposition. This cytokine has also been shown to upregulate Smad7 in chondrocytes.[46] No studies have reported the Smad7 or TGF-β signature in HFE-mutated chondrocytes, as opposed to hepatocytes. One group in Canada have found high levels of the matrix metalloproteins[1,3,13] iNOS and COX-2 in cultured chondrocytes from knee tissue removed at the time of arthroplasty in GH patients vs OA controls, and also a similar increase in these proteins in normal chondrocytes transfected with mutated HFE gene irrespective of iron concentration in the culture medium.[47] Further demonstration of an effect of the mutated HFE protein on chondrocyte function, leading to a hepcidin-/

iron-independent accelerated OA phenotype would thus start to explain these conundrums. The hypothesis being that dysfunction would be maximally expressed in people with the C282Y mutation where the HFE protein is not expressed on the cell surface, and also seen in H63D mutations where the effect is mediated by disrupted ligand binding, with similar consequences.

Conclusion

The low penetrance of GH to iron overload has remained incompletely explained, now 22 years after the gene mutation was recognised and the link to hepcidin deficiency was subsequently established.[2] Pattern recognition remains an important tool of the practicing clinician, notwithstanding the assistance provided by ever-expanding technologies to assist the diagnostic process. The arthropathy of haemochromatosis has a specific pattern akin to an accelerated OA phenotype with characteristic features, and long recognised to present anomalies with respect to the other manifestations of GH in iron overloaded cases. Whilst the lack of efficacy of 'de-ironing' to improve joint symptoms and prevent progression to unaffected joints might be explained by (but lacks evidence for) a sequestered role of iron in the joint, it is the occurrence of clinically classic haemochromatosis arthropathy in non-iron overloaded cases, with both major and minor HFE mutations, that poses the most intriguing questions. The recognition of these conundrums opens the door to research to link the HFE protein to cartilage homeostasis, which might not just explain the arthropathy of GH but add to our understanding of the aetiopathogenesis of primary OA, which this condition resembles in an accelerated phenotype.

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