Characteristics of the Arthropathy Described in Hereditary Hemochromatosis

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Introduction

Hereditary hemochromatosis (HH) is a common inherited metabolic disorder characterized by systemic iron overload (1,2). HH affects approximately 1 in 200 people and is most common in persons of Northern European origin. Organ damage in the pancreas, liver, heart, endocrine glands, skin, and joints has been described in HH. There is evidence that the frequency and extent of organ damage may be changing with time, perhaps due to earlier diagnosis and treatment (3). In persons of Northern European origin, homozygosity for the C282Y mutation in the HFE gene found on chromosome 6 is present in more than 90% of patients with unequivocal HH (4), whereas in Southern Europe, as many as 30% of cases may be heterozygous or wild type for this mutation (5).

The clinical manifestations of the disorder were first comprehensively reviewed by Sheldon in 1935, but interestingly, in his description, an arthropathy is not recorded (6). It was not until Schumacher described 2 cases and reported a peripheral arthritis in 5 of 23 hospital cases of idiopathic hemochromatosis in 1964 that arthropathy was identified in hemochromatosis (7). Subsequent studies have confirmed the presence of a clinically recognizable arthropathy (8–17). Although clinically and radiologically characteristic and highly suggestive of the joint disorder often found in HH, the arthropathy is not specific for hemochromatosis, since it cannot be differentiated from monarticular osteoarthritis (OA) in the same target joints or from the form of polyarticular OA provisionally classified as the type 2 polyarticular OA phenotype, an example of which is depicted in Figure 1 (18,19). Moreover, differentiation from pyrophosphate deposition disease, diabetes mellitus with metacarpophalangeal (MCP) joint involvement, and even rheumatoid arthritis (RA) can sometimes be difficult (8,20).

Characteristics of the arthropathy

Frequency of arthropathy. The exact proportion of patients who manifest an arthropathy is unknown. Arthropathy in HH has been reported to range from 24–81% (Table 1). Most of these frequency estimates are derived from retrospective case series, where more severe cases of HH tend to be concentrated. The investigations performed by Bulaj et al, however, are particularly salient (21). They evaluated clinically unselected C282Y homozygous relatives of HH probands and determined by radiologic assessment the frequency of MCP joint arthropathy in those with demonstrable iron overload. MCP joint arthropathy, compatible with that attributable to HH, was detected in 17 (15%) of 113 male C282Y homozygous relatives with iron overload and in at least 6 (8.7%) of 69 female C282Y homozygous relatives with iron overload. These observations are very similar to those obtained by Carroll et al in a study of HH and non-HH participants who were recruited by newspaper advertising without disclosure of an arthritis research focus, where 3 (13%) of 23 men with definite or probable HH had finger MCP joint arthropathy, as did 3 (16%) of 19 women (17). However, when bilateral arthropathy in other putative target joints such as the radiocarpal, elbow, hip, knee, or ankle joints was also applied as a criterion for the diagnosis of a compatible arthropathy, the frequency of arthropathy was found to be 25% in participants with definite or probable HH, whereas in possible or unlikely HH the frequency was just 3%. The association observed between arthropathy, homozygosity for C282Y, and mobilizable iron stores determined by historic phlebotomy requirements suggests that iron load is a major determinant of arthropathy in HH and more important than occupational factors (16). Likewise, 2 other studies have also reported that arthropathy in HH is strongly associated with iron load (15,16).

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Considerable variation in the frequency of chondrocalcinosis has been reported, with estimates ranging from 5–49% of study participants (9–11,13–15,17). Factors likely to account for this variation include recruitment methods (tertiary hospital clinics versus community recruitment) and radiograph protocols (clinically involved joints versus skeletal radiograph survey). Since chondrocalcinosis is considered to be a late manifestation of the disease, disease chronicity is also likely to influence the findings. In a 10-year followup study, Hamilton et al found that the frequency of chondrocalcinosis increased from 39% to 72% in 18 patients with well-characterized HH and known arthropathy who were undergoing regular venesection (22). Therefore, regular venesection and iron depletion did not appear to prevent the development of chondrocalcinosis. In no patient was diminution in size or disappearance of the chondrocalcinosis observed over time. Moreover, in 12 of the 13 patients who developed chondrocalcinosis, 2 or more joints were affected, which is consistent with the possibility that chondrocalcinosis is a predictor of either more severe or more extensive joint disease.

Joints affected: topography. The arthropathy of hemochromatosis is a chronic progressive arthropathy. The index MCP (MCP2) and middle finger MCP (MCP3) joints are most commonly affected in HH. These joints are also affected in some patients with juvenile HH, which has a distinctly different genetic basis (23). The involvement of the MCP2 and MCP3 joints can be appreciated on clinical examination. Typical findings include hard tissue and soft tissue swelling and in more advanced cases, reduced range of movement. Limited passive flexion (maximum less than 70 degrees) in the authors' experience is particularly suggestive of MCP2 and MCP3 joint damage. The limited flexion accounts for the "iron fist" sign, an example of which is shown in Figure 2 (24).

Among 54 male patients with idiopathic hemochromatosis, 31 of whom had arthropathy, Dymock et al found that the frequency with which the MCP4 and MCP5 joints were affected was 23% and 14%, respectively (9). Some clinicians consider that involvement of the more lateral MCP joints increases the probability of hemochromatotic arthropathy. Other joints in the hands can be affected in HH, but usually in association with the MCP2 and MCP3 joints. These include the interphalangeal joints of the fingers. Coexistent interphalangeal joint disease due to OA can be difficult to exclude and may account for these findings. Carroll et al found that the frequency of Heberden's nodes and the frequency with which a priori criteria for primary idiopathic OA in the interphalangeal joints (type 1 polyarticular OA) were met was the same in HH patients and community controls deemed unlikely to have HH (17). A trend toward more frequent involvement of the triscaphe (scaphoid–trapezoid–trapezium) joint was noted by Valenti et al (15). Occasionally, the wrist and intercarpal joints can be affected (7,15). However, none of these joint changes is specific for HH. Where chondrocalcinosis is present in either articular cartilage or fibrocartilage in association with a compatible MCP2 and MCP3 joint arthropathy, the specificity for the arthropathy of HH may be very high, but to our knowledge this hypothesis has not been formally tested.

The large joints such as the hip, ankle, radiocarpal, elbow, shoulder, and knee joints are also recognized sites in which the arthropathy of HH may manifest (8,9,11,13,15). Joints such as the ankle and radiocarpal joints, which are usually spared in idiopathic or primary OA, when affected and especially if involved bilaterally, confer a greater probability for the arthropathy of HH than, for example, similar findings in the knee joint. To date, however, no clinical criteria based on topography alone have been tested for diagnostic sensitivity and specificity for HH.
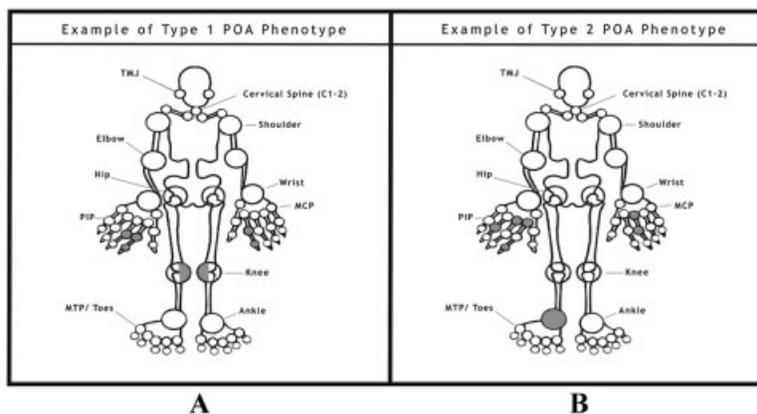

Figure 1. Examples of type 1 (**A**) and type 2 (**B**) polyarticular osteoarthritis (POA) phenotypes. TMJ = temporomandibular joint; PIP = proximal interphalangeal; MCP = metacarpophalangeal; MTP = metatarsophalangeal.

Table 1. Frequency of arthropathy and chondrocalcinosis in reported series of patients with hemochromatosis and arthropathy*

Author, year (ref.)	Arthropathy	Chondrocalcinosis	% males in study
Dymock et al, 1970 (9)	57.4% (n = 54 males)	49.2%; 64.0% with arthropathy	93.1
Edwards et al, 1980 (10)	37.1% (n = 35)	17.1%; 46.2% with arthropathy	60.0
Huaux et al, 1986 (11)	56.0% (n = 25)	20.0%; 28% with arthropathy (n = 20)	72.0
Schumacher et al, 1988 (12) (questionnaire study, frequency of arthralgias)	81.1% (n = 159)	NA	64.2
Faraawi et al, 1993 (13)	64% (n = 25)	36%	72.0
Sinigaglia et al, 1997 (14)	81.3% (n = 32); note that 31.2% had disease-specific arthropathy	6.3%	
Valenti et al, 2008 (15)	36% for MCP joint disease (n = 88)	11%; 100% with arthropathy (n =10)	80.7
Richette et al, 2010 (16)	51% (OA in any of 7 regions) (n = 306)	NA	52.6
Carroll et al, 2011 (17)	24.4%; 14.6% with MCP joint arthropathy (n = 41)	4.9%; 100% with arthropathy (n = 2)	43.9

* NA = not applicable; MCP = metacarpophalangeal; OA = osteoarthritis.

Is the arthropathy inflammatory or noninflammatory? The arthropathy of HH is generally considered to be non-inflammatory. Despite the frequency of chondrocalcinosis, pseudogout presentations are uncommon. Case series draw attention to occasional cases where impressive clinical signs of an inflammatory reaction have been observed and occasionally aspirates have disclosed numerous inflammatory cells and/or calcium pyrophosphate dihydrate (CPPD) crystals, but synovial fluids are mostly noninflammatory. As in idiopathic OA, a clinically apparent inflammatory component to the arthropathy may sometimes be evident and may fluctuate in intensity over time. The observation that ferritin concentrations in the synovial fluid are higher in patients with OA who have HFE gene mutations raises the possibility that ferritin may be a marker for an inflammatory component in the arthropathy of HH and possibly also in OA (25).

Radiologic findings in the arthropathy of HH. The radiologic features of the arthropathy of HH are similar to those in idiopathic OA (26,27). Subchondral sclerosis and joint space narrowing are typical. The latter can be rapidly progressive with substantial deterioration within a matter of months (11). More often, however, the rate of progression is relatively slow. Osteophytes may be present and can be prominent. In the MCP2 and MCP3 joints, hook-like osteophytes on the radial side of the metacarpal heads are characteristically seen. In our study, they were present in 17% of 41 definite or probable HH cases, all of whom were homozygous for the C282Y mutation (17). Although hook-like osteophytes are regarded as a characteristic feature of the arthropathy of HH, they also occur in OA and are thus not disease specific. In many studies, attention has been drawn to 2 particular radiologic features of the arthropathy described in HH, notably subchondral lucencies and chondrocalcinosis. The frequency with which subchondral lucencies or geodes are found in joints affected by the arthropathy accompanying HH is high. Dymock et al described a strong correlation between subchondral lucencies and focal or eccentric chondral resorption and noted that cartilage loss occurred only occasionally in the absence of lucencies (9). Lucencies may be prominent in the hip joint (28) (Figure 3). Erosions such as those seen in RA are not present, although infraction of marginal subchondral lucencies may be difficult to discriminate from rheumatoid erosions.

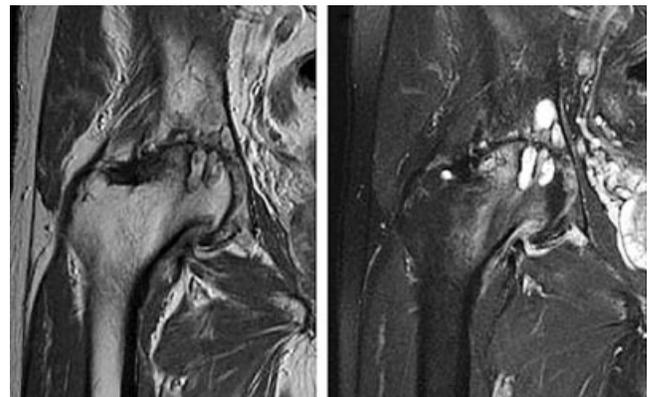**Figure 2.** An example of the "iron fist" sign.

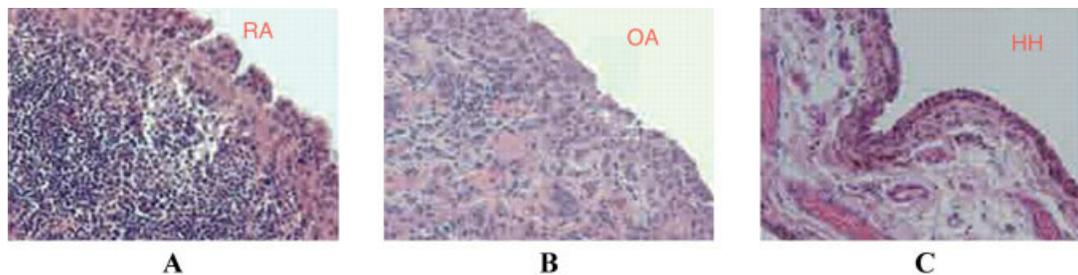**Figure 3.** Lucencies showing prominence in the hip joint.

Figure 4. Pathology of the arthropathies of **A,** rheumatoid arthritis (RA), **B,** osteoarthritis (OA), and **C,** hereditary hemochromatosis (HH).

Chondrocalcinosis has been reported variably (Table 1). It may involve articular and nonarticular cartilage. Common sites include the knee in both meniscal and articular cartilage, other large joints, and the wrist, particularly in the triangular fibrocartilage. The symphysis pubis and spine may also be involved. Chondrocalcinosis may be detected in both clinicoradiologically involved and uninvolved joints.

Pathology and etiopathogenesis of arthropathy in HH

Most of the information concerning joint pathology in HH has been obtained from surgical specimens derived at the time of joint replacement surgery, and is therefore representative of advanced disease. Various pathologic findings have been described. Thinning or erosion of articular cartilage with exposure of eburnated bone is commonly described, but other findings such as iron deposition in cartilage, chondrocalcinosis, primary and secondary osteonecrosis, and articular cartilage avulsion at the tidemark in hip cartilage have been observed in some studies, although not others (29,30). Cartilage avulsion is a very unusual finding in primary OA (29).

In the synovium, deposits of iron have been observed, particularly in the synovial lining cells (6,7,31–33). Indeed, deposition here as opposed to in the sublining layers or synovial stroma differentiates between HH and secondary forms of hemochromatosis, such as occurs in thalassemia major (34). In the latter, sublining deposition is more marked (31). In a recently published report, Heiland et al describe the differences in synovial tissue obtained from joint replacement specimens in patients with RA, OA, and HH (32). They note many common features and very few differences overall between synovial tissue in OA and that in hemochromatotic arthropathy. In the arthropathy of HH, there was more pronounced infiltration of macrophages and neutrophils. Importantly, hemosiderin deposits were found only in HH and not the RA or OA synovium. Macrophage and neutrophil infiltration was correlated with the degree of hemosiderin deposition. Interestingly, hemosiderin was still present in HH patients who had undergone regular venesection. The authors emphasize that HH arthropathy can be clearly differentiated from OA by the infiltration of cells of the innate immune response (macrophages, neutrophils), and also from RA by the lack of infiltrating specific immune cells (B cells, T cells). Therefore, in a number of respects, the pathology of the arthropathy of HH is distinguishable and "intermediate" between that of RA and OA (Figure 4).

How iron is deposited and accumulates in the synovium in patients with HH is unclear, but the predominance of iron in the synovial lining layer raises the possibility that iron may be "captured" from the synovial fluid as a result of persistently high serum ferritin concentrations and the phagocytic actions of synovial fibroblasts. Deposition may be effectively irreversible and accompanied by slowly progressive chondral resorption, even in subjects who undergo regular venesection (12,32). Iron deposition may itself be seriously detrimental to the joint. Ferritin has recently been shown to act as a proinflammatory cytokine and could contribute directly to joint injury (35). Importantly, in hepatic stellate cells, at nanomolar concentrations similar to those observed by one of the authors (GJC) in synovial fluid in HH, ferritin was found to be a potent and rapid inducer of interleukin-1 gene expression (35).

How excess iron contributes to the development of calcium pyrophosphate production and chondrocalcinosis is not well understood. In vitro studies show that iron inhibits pyrophosphatase, suggesting that excess iron may promote pyrophosphate deposition in the synovium or cartilage (36). Additionally, accumulation of calcium pyrophosphate may be facilitated by reduced clearance in the setting of synovial siderosis (37). Whereas both ferric and ferrous iron influence CPPD formation, to date chondrocalcinosis has not been definitively linked to the level of iron overload (38,39).

Prognosis and treatment

Arthropathy in HH may predate other manifestations of the disease and is sometimes the manifestation that leads directly to diagnosis. Even when recognized early, there is conjecture as to whether subsequent iron depletion has any effect on the symptoms of the arthropathy or its course. There are anecdotal descriptions of symptom relief following phlebotomy and in one survey, approximately one-third of patients indicated that they experienced improvement in musculoskeletal symptoms following iron depletion (7,40,41). Most authorities doubt that phlebotomy produces any substantial relief of arthralgias or other joint symptoms (8–12,31,42). Moreover, it appears unlikely that "de-ironing" has any effect on structural progression of the joint disease, which appears to be inexorably progressive and irreversible. In contrast, other manifestations of HH are much more responsive to iron depletion, so much so that arthropathy is now considered to be the main cause of morbidity and reduced quality of life in treated disease. Whether "tight control of iron metabolism" from an early age in those considered likely to

manifest clinically overt HH could prevent arthropathy altogether, or at least produce better outcomes, is unknown.

Other forms of medical treatment for the arthropathy of HH have been utilized. Analgesics, nonsteroidal antiinflammatory drugs, and coxibs can produce symptomatic relief, but they are not thought to have any disease-modifying effects, although no formal studies have been undertaken. Clinician use of synthetic (nonbiologic) "anti-rheumatoid" agents either empirically or due to diagnostic error suggests no obvious benefit. Intraarticular steroids may be useful temporarily, but are generally unpredictable (Carroll G: unpublished observations). To our knowledge, there are no published studies on the effects of anticytokine therapy. There is scope for major benefit from surgical interventions in HH arthropathy, especially joint arthroplasties. A comprehensive review of surgical interventions is outside the scope of this review.

Discussion

The arthropathy of hemochromatosis is relatively common, even in patients with HH recruited from the community. It is a chronic progressive arthropathy with a level of inflammatory activity that is both clinically and histopathologically intermediate between that of RA and OA. There is a predilection for the finger MCP joints and it is variably accompanied by chondrocalcinosis. The precise mechanism responsible for tissue damage in affected joints remains unknown; however, there is growing evidence that iron load is a major determinant of the arthropathy. HH arthropathy does not usually respond to venesection, but whether tight control of iron metabolism from an early age could produce better outcomes remains to be determined. Novel approaches to management with a view to prevention of structural joint damage still need to be developed.

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