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ORPHAN DISEASES (B MANGER, SECTION EDITOR)

HFE-Related Hemochromatosis: An Update for the Rheumatologist

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Abstract Hereditary hemochromatosis is a frequent disease in Caucasian populations. It leads to progressive iron overload in a variety of organs. The most common cause is the C282Y homozygous mutation in the HFE gene. The classical triad of skin hyperpigmentation, diabetes, and liver cirrhosis is nowadays rare but musculoskeletal symptoms are common in HFE-related hemochromatosis. Typically the second and third metacarpophalangeal joints, and the wrist, hip, and ankle joints are affected. Clinical symptoms include osteoarthritis-like symptoms, pseudogout attacks, and synovitis sometimes resembling rheumatoid arthritis. Radiographs show degenerative changes with joint space narrowing, osteophytes, and subchondral cysts. Chondrocalcinosis in the wrist and knee joints is seen in up to 50 % of patients. Although most other organ manifestations regress during phlebotomy, musculoskeletal symptoms often persist or even become worse. Importantly, patients are at an increased risk of severe large-joint arthritis necessitating joint replacement surgery. Therefore, future research should focus on the pathogenesis and treatment options for HH arthropathy.

Keywords Hemochromatosis · HFE gene · Iron overload · Arthropathy · Chondrocalcinosis · Diagnosis · Clinical presentation · Screening

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Introduction

HFE (High Iron Fe)-related hemochromatosis (HH) is a systemic disorder leading to iron overload in parenchymatous organs, eventually causing organ failure and death [1]. Skin hyperpigmentation, diabetes and liver cirrhosis is the classically described triad of HH, although rare in clinical practice nowadays, most likely because of earlier recognition of this condition [2]. HH has attracted much interest since the identification, in 1996, of the causative mutation which is responsible for most cases [3]. Research on the epidemiology and penetrance of this gene mutation has progressed. Also, experimental studies have provided important insights into the pathophysiology of iron overload in HH. Further, recent studies have focused on musculoskeletal manifestations of HH and their consequences, which will be the major focus of this review.

Genetic Cause and Penetrance of HH

Hereditary hemochromatosis has long been known as a genetic disorder primarily occurring in Caucasians. It is associated with systemic iron overload and potentially lethal outcome [4]. Most HH cases result from a variation of the HFE gene located on chromosome 6, and more than 80 % of patients of northern European descent are homozygous for HFE mutation C282Y [3, 5, 6]. Its prevalence in Caucasians is approximately 0.5 % and its inheritance is autosomal-recessive [7]. In other populations, for example indigenous African or Asian, the mutation is basically non-existent [8, 9]. In some of these populations, the H63D mutation (His to As) can be found frequently. Homozygous H63D mutations alone are, however, not sufficient to induce iron overload [10]. A homozygous C282Y is strongly associated with HH development whereas "compound heterozygosity" of C282Y and

H63D causes HH only in the presence of other risk factors [11]. HFE-related hemochromatosis is now referred to as type 1 hemochromatosis.

In the first years after the discovery of the HFE mutation, the penetrance of the C282Y homozygous mutation was probably over-estimated. Phenotypic expression of the C282Y mutation seems to be very low in women and moderate in men. In family-based screening, elevated liver enzymes were observed in fewer than 30 % of male homozygotes and liver cirrhosis was present in only 6 % of males and 2 % of females [12, 13]. In a population-based study from Australia, the proportion of iron overload-related disease was 28 % in men and 1 % in women [14]. In addition to environmental factors, for example diet, alcohol consumption, and coexisting chronic viral hepatitis, the phenotype of hemochromatosis may be further modulated by host factors such as gender, age, obesity, and additional genetic variants [15–18]. It has recently been suggested that gene polymorphisms in other genes relevant to iron metabolism, for example TMPRSS6, are involved in the penetrance of HFE-related hemochromatosis [19].

In contrast with HFE-related hemochromatosis, other rare mutations have been described; these cause mainly juvenile and severe forms of hereditary hemochromatosis. Types 2A and 2B are caused by mutation of the hemojuvelin (HJV) gene and the HAMP (Hepcidin antimicrobial peptide) gene, respectively [20, 21]. These mutations are responsible for juvenile hemochromatosis and the inheritance is autosomal-recessive. Type 3 hemochromatosis is caused by a mutation in the transferrin receptor 2 (TRF2) gene [22]. The inheritance is autosomal-recessive also. Type 4 hemochromatosis is very rare and caused by mutations in the SLC40A1 gene encoding the ferroportin gene (Ferroportin disease) [23, 24]. The disease can be grouped into two clinically distinct subtypes (types A and B). Type B is phenotypically similar to types 1–3 hemochromatosis whereas type A is characterized by low transferrin saturation levels and a distinct iron accumulation in the liver. Both forms are autosomal-dominant inherited.

Pathophysiology of Iron Overload

In recent years, significant progress has been made in our understanding of the pathophysiology of HFE-related hemochromatosis. Intestinal iron absorption and distribution is regulated by a hepatic iron-sensing complex, composed of the HFE-protein, TFR2 and HJV [25]. Adequate body iron stores are recognized by this complex, subsequently leading to an increase of hepcidin (hepatic bactericidal protein) production. Hepcidin, a 25-amino-acid peptide hormone identified in 2000, is a master regulator of systemic iron metabolism [26]. Systemic iron homeostasis is maintained in a hormone-like negative feedback mechanism. Hepcidin is secreted from hepatocytes in response to iron overload, inflammation, hypoxia, or anemia [27]. Hepcidin exerts its regulatory functions on iron homeostasis via binding to the only known iron exporter, Ferroportin (FPN), thereby leading to FPN phosphorylation, degradation, and consecutively to blockage of cellular iron export, which induces a decrease in serum iron [28]. Lack of hepcidin expression consequently causes uncontrolled iron resorption from the gut [29].

It seems that lack of proper HFE protein production in C282Y homozygous individuals causes disturbance of the aforementioned iron-sensing complex. This leads to reduced hepcidin production, which in turn causes uncontrolled intestinal iron resorption [30]. Elegant experimental studies on rodents confirm this hypothesis. Lack of duodenal HFE expression does not cause disturbed systemic iron metabolism whereas hepatic HFE deletion causes iron overload in mice [31, 32]. Consequently, hepcidin treatment of HFE-deficient mice reverses iron overload [33]. For humans, liver transplantation corrects inadequately low hepcidin levels in C282 homozygous patients with end-stage liver disease [34•]. Conversely, transplantation of a C282Y homozygous liver donor can cause hemochromatosis in the recipient [35].

Clinical Presentation, Diagnosis, and Screening

Many symptoms of HH caused by iron overload are rather common and unspecific. Usually, iron overload slowly develops in type 1 hemochromatosis and first causes symptoms in middle-aged individuals. Fatigue, arthralgias, diabetes, and evidence of chronic liver disease are frequent in HH [36]. Liver disease is often rather mild and present as elevated transaminases but may also progress to liver cirrhosis and development of hepatocellular carcinoma in a subset of patients. Hypogonadism, cardiomyopathy, adrenal insufficiency, porphyria cutanea tarda, and others can be manifestations of HH.

Routine screening for HFE-related hemochromatosis is not recommended, because of the low penetrance of the known mutations, although the C282Y allele is present in approximately 4 % of the German population, for instance [6]. Thus, iron status should be checked when iron overload is suspected, for example in patients with unexplained liver disease, arthralgias, chondrocalcinosis, cardiomyopathy, or porphyria cutanea tarda. In addition, genetic counseling and family screening of individuals with hereditary hemochromatosis is strongly recommended, especially for siblings [37].

Diagnosis of HFE-related hemochromatosis is usually based on fasting serum ferritin levels and transferrin saturation levels. Recent clinical practice guidelines of the European Association for the Study of the Liver (EASL) suggest genetic testing of the HFE gene when transferrin saturation was twice >45 % [37]. Diagnosis of type 1 hemochromatosis should be

reserved for individuals with C282Y homozygosity or compound heterozygosity and evidence of iron overload. If HFE testing furnishes negative results, other causes of iron overload and hyperferritinemia and the possibility of non-HFE hemochromatosis should be evaluated.

Hemochromatosis Arthropathy

Clinical Presentation

Articular pain is common in hemochromatosis, but was not established as a major feature until 1964 [38]. HH arthropathy affects up to two-thirds of patients [39]. It can precede other HH symptoms and might even lead to diagnosis [40]. Therefore, knowledge of the specific features of HH arthropathy is relevant. Even though HH may cause symptoms similar to those of other rheumatic disorders, there are important differentiating features, for example age at onset, location, and gender preference. The true association of iron overload and musculoskeletal problems is emphasized by the fact that juvenile hemochromatosis patients also develop arthropathy [41]. Further, transfusion-related iron overload may also cause an arthropathy similar to HH [42].

HH can cause a variety of musculoskeletal symptoms in affected individuals. Clinical presentation may range from typically degenerative joint pain similar to that of idiopathic OA to monarthritis or oligoarthritis, from recurrent pseudogout attacks to presentations difficult to distinguish from rheumatoid arthritis. However, OA-like symptoms are, in clinical practice, the most frequent presentation [43, 44••]. HH, as opposed to idiopathic OA, typically affects men, and the topography of the affected joints also differs. Classic locations of HH are the second and third metacarpophalangeal joints, which are rarely affected in idiopathic OA [45]. However, other affected joint regions in HH, for example the knee and hip joints and the wrists, are also involved in other rheumatic disorders. Bilateral ankle joint involvement is typical for HH, but its prevalence is rather low [46]. Symmetric involvement of affected joints is very common in HH [44••].

HH arthropathy of the hands is slightly milder than idiopathic hand OA and patients present with better hand function and less tender joints [45]. This is possibly based on the joints predominantly affected by HH. Idiopathic hand OA more often leads to involvement of the CMC joint and the distal IP joints than HH. However, these joints seem to be more important for hand function than MCP joints, which are more often affected in HH patients [47]. Nonetheless, subjective pain levels are similar in the two conditions. Typically, HH patients present with tender and sometimes swollen bilateral MCP2 and MCP3 joints [48]. The other MCP joints can be affected but are often not strikingly involved. Sometimes, HH patients present with synovitis of the MCP joints, which could be mistaken for rheumatoid arthritis. Therefore, serum ferritin levels and liver chemistry should be checked for such patients for differential diagnosis. Degenerative arthritis of other finger joints is present in HH, but indistinguishable from that of idiopathic OA.

Large joint involvement in HH is frequent and not a mild disease. Several studies, including population-based studies, have independently shown that HH patients are at increased risk of developing severe hip and, possibly, also knee-joint OA, often necessitating joint replacement surgery [49•, 50, 51•, 52] (Table 1). Ankle joint involvement, although rare, causes severe problems, because joint-replacement surgery is still not as advanced as for other large joints. Chondrocalcinosis is a frequent finding in the wrist and knee joints of HH patients. Nevertheless, true pseudogout attacks are infrequent in clinical practice and most HH patients report OA-like symptoms.

Osteoporosis has been described in patients with hereditary hemochromatosis. However, lower bone mineral density and bone fragility might be caused by other organ manifestations of HH rather than being directly linked to iron toxicity itself. Osteoporosis could be because of hypogonadism and advanced liver disease, which are well-known causes of secondary osteoporosis [53]. In contrast, some clinical data suggest that osteoporosis may occur in the absence of gonadal or liver disease in HH [54, 55].

Risk Factors

Although arthropathy is frequent, there are many HH patients with significant iron overload-related disease that do not develop musculoskeletal symptoms. Therefore, identification of risk factors for this clinically relevant disease manifestation is warranted. Iron overload itself, measured as magnitude of serum ferritin levels at diagnosis, was associated with the presence of arthropathy in two studies; another study found no evidence for such as an association [44••, 48, 52]. Female gender, MCP joint involvement, and the presence of chondrocalcinosis were associated with severe disease necessitating large joint replacement surgery in one study [44••]. Recently, serum levels of vascular adhesion molecule 1 (VCAM-1) emerged as a potential biomarker for HH arthropathy [56].

Laboratory Signs in HH Arthropathy

As mentioned above, type 1 hemochromatosis patients typically have highly elevated transferrin saturation, and serum ferritin levels—depending on the stage of the disease—ranging from normal to highly elevated [37]. Liver transaminases are usually only mildly elevated. Serum ferritin levels above 1,000 $\mu g\ L^{-1}$ in HH patients are closely associated with clinical and laboratory symptoms [57].

Table 1 Clinical studies showing the increased risk of joint failure in hereditary hemochromatosis

Authors	Type of study	Participants (*n*)		Joint-replacement surgery risk (95 % CI)	
		Cases	Controls	Knee	Hip
Sahinbegovic et al. [49•]	Case–control	199	824	OR 9.0 (4.6–17.4)[a]	
Richette et al. [52]	Case–control	306	304	OR 5.3 (1.1–25.6)	OR 5.2 (2.2–11.9)
Wang et al. [50]	Population-based cohort	184	27,664	HR 0.51 (0.16–1.57)	HR 1.94 (1.04–3.62)
Elmberg et al. [51•]	Population-based cohort	3,531	11,794	HR 2.14 (1.58–2.88)	HR 2.77 (2.27–3.38)

[a] Combined results for knee and hip joint-replacement surgery

[b] Reported as physician-diagnosed OA

[c] Reported as hospitalization for OA

OR, odds ratio; HR, hazard ratio

Though synovitis may be present in HH arthropathy patients, elevated inflammation markers, for example erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are observed only occasionally. Rheumatoid factor might be positive in some patients with HH, but this is likely to be because of advanced liver disease in these patients and usually of low-titer. Anti-citrullinated peptide antibodies (ACPA) were negative in all but one asymptomatic patient in a cross-sectional study of 87 HH individuals [58].

Radiographic Features of HH Arthropathy

Conventional X-ray radiography is the standard method for detecting structural changes associated with HH arthropathy. There are no findings exclusive to HH arthropathy. Rather, the combination of radiographic signs can be suggestive of HH-related musculoskeletal disease (Table 2). A typical picture can be found in hand X-rays: predominant involvement of the second and third MCP joint, with joint space narrowing, subchondral cysts, and formation of hook-like osteophytes at the radial side are suggestive for HH arthropathy (Fig. 1) [59]. Marginal erosions are sometimes detected in HH arthropathy. Interestingly, joint involvement in the hands of HH arthropathy is strongly symmetric. A radiographic scoring system for HH arthropathy has recently been developed [60].

Chondrocalcinosis (CC) is a frequent feature found in 30–50 % of HH patients. Its location is no different from CC of other origin, with occurrence most often in the wrists and knee joints [60]. Sometimes, CC can be found in MCP joints and ankle joints in severe cases of HH arthropathy. Whether or not CC is crucial for the development of HH arthropathy is currently unknown, but classical arthropathy can develop without cartilage calcification. In the large joints, including the hip, knee and ankle joints, typical signs of degenerative arthritis can be found in HH arthropathy [44••]. In the hip, aseptic necrosis of the femoral head has been described rarely [61].

Table 2 Radiographic features of hemochromatosis arthropathy

Hook-like osteophytes (MCP joints)
Joint space narrowing
Subchondral cysts
Marginal erosions
Chondrocalcinosis (frequent: wrist, knee; rare: MCP joints, ankle joints)
Femoral head necrosis (rare)

There are hardly any systematic studies reporting MRI findings for HH arthropathy. Recently, Frenzen et al. reported on 49 patients with hemochromatosis undergoing low-field MRI investigation of the hand [62]. Findings included synovitis, erosions, bone marrow edema, and degenerative changes, emphasizing the destructive nature of this disease in a subset of patients. There are no studies systemically reporting sonographic features of hemochromatosis arthropathy.

Pathophysiology of HH Arthropathy

It is yet not clear how iron overload damages joints in HH. Histological specimens of synovial tissue show many similarities between OA and HH arthropathy but also some distinctions [63]. The latter features more macrophages and neutrophils, their infiltration probably being a reaction to hemosiderin found in the same place. Very few B or T-cells could be found in the synovial tissue. However, this was a study using synovial tissue from patients undergoing joint-replacement surgery. Therefore, these findings do not preclude intermittent inflammatory phases in HH patients in earlier disease phases. Another study investigated ferritin levels in synovial fluid of idiopathic OA patients with or without heterozygous HFE mutations [64]. Patients with C282Y or H63D mutations had higher ferritin concentrations in the synovial fluid. Because ferritin is too large to pass from serum into the joint cavity, the high concentration in the cavity might result from local production. Another possibility may be retention of iron by sequestered cells. Local iron overload may therefore

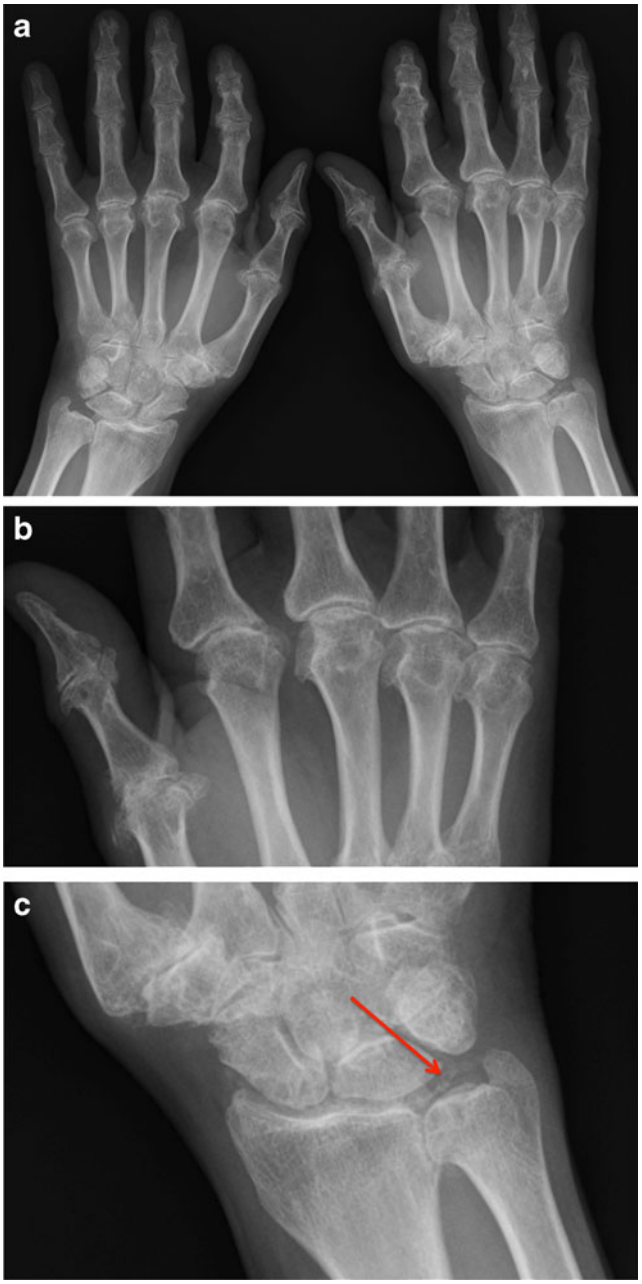

Fig. 1 Hemochromatosis arthropathy. Conventional X-ray of the hands showing severe degenerative arthritis in a 76-year-old male patient with HFE-related hemochromatosis: involvement of the MCP joints with joint space narrowing, subchondral sclerosis, hook-like osteophytes (**a**, **b**). Severe OA of the interphalangeal joints and thumb OA is also detectable. Chondrocalcinosis is present in the wrist (*arrow*, **c**)

contribute directly to joint damage. However, iron accumulation in the synovium is not a feature of hemochromatosis arthropathy only.

Therapy and Outcome

Left untreated, hereditary hemochromatosis may ultimately lead to death from liver cirrhosis, hepatocellular carcinoma, or cardiomyopathy. Phlebotomy to remove excess iron, if started before end-stage organ failure occurs, normalizes life expectancy, can even reverse severe liver damage, and is usually well tolerated [65]. Initially, venesection is performed weekly by removing 400–500 mL blood (200–250 mg iron) to achieve a low level of ferritin (<50 μg L^{-1}). To maintain this level, venesection every two to six months is then performed.

HH arthropathy has, unfortunately, a distinct reaction to therapy. Joint pain may improve, be unchanged, or be aggravated in the first months after the start of therapy [39]. Surprisingly, HH arthropathy can even develop after the initiation of phlebotomy treatment. Overall, most patients are not satisfied with the effects of phlebotomy on musculoskeletal symptoms in clinical practice. In agreement with this, a study showed that serum levels of markers of type II collagen production and degradation, increased after depletion of iron in HH patients [66]. The authors speculate that articular cartilage may be especially sensitive to iron mobilization.

Therapy for HH arthropathy in general is based on knowledge of treatment of idiopathic OA. Pain relievers, for example acetaminophen and non-steroidal anti-rheumatic drugs, are frequently used. For patients with chondrocalcinosis and inflammatory arthritis, colchicine can be used to prevent recurrent pseudogout attacks [67]. Both monosodium urate crystals found in gout and calcium pyrophosphate dihydrate (CPPD) crystals responsible for chondrocalcinosis and pseudogout have been found to engage the so-called NALP3 inflammasome [68]. Activation of this pathway leads to a strong pro-inflammatory reaction with production of Interleukin-1 (IL-1) and other mediators. Anakinra, an IL-1 antagonist, has been shown to be efficacious in the treatment of gout and there are case reports of refractory patients with CPPD deposition disease responding to anakinra treatment [69]. Recently, Latourte et al. successfully treated two patients with severe hand arthropathy due to HH by use of anakinra [70•]. The patients reported rapid pain relief and improvement of disability and the signs of inflammation disappeared. After discontinuing anakinra, the symptoms returned. Future studies are warranted to investigate the role of IL-1 antagonism in the treatment of HH arthropathy. Currently, treatment of HH arthropathy remains unsatisfactory.

Conclusions

Significant progress has been made in our understanding of the pathogenesis of iron overload in HFE-related hemochromatosis. Arthropathy is a common feature of HH but its pathogenesis is poorly understood. The clinical manifestations and consequences of musculoskeletal disease in HH have been delineated. Future research should focus on understanding the evolution of HH arthropathy, which could lead to the development of specific treatments.

Compliance with Ethics Guidelines

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Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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- •• Of major importance

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