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Genetic haemochromatosis is a hereditary disease characterised by tissue iron overload. In Caucasians it is most often due to homozygous C282Y HFE gene mutation, but other genes may be involved. Without treatment by venesections, patients can develop life-threatening visceral damage such as liver cirrhosis and carcinoma, diabetes or heart failure. This treatment has been remarkably successful in preventing these complications, but patients survive with other symptoms of the disease susceptible to impair, sometimes seriously, their quality of life. This is the case of arthropathy and osteoporosis complicating haemochromatosis. In this chapter, focus has been placed on the rheumatological complications of genetic haemochromatosis.

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blood removal. However, despite treatment by phlebotomies, patients’ quality of life is often altered by the rheumatological conditions of the disease, particularly joint symptoms and sometimes osteoporosis. That is why rheumatologists are in first line to diagnose the disease and to treat bone and joint damage.

**Genetics and physiopathology**

GH was originally reported by Trousseau in 1865 [1]. The major finding was the presence of a triad associating cirrhosis and diabetes in a tanned man. The picture of the disease has been progressively completed until now. Von Recklinghausen reported, in 1889 [2], the presence of strong iron deposits within the liver of those patients, thus leading him to evoke the role of iron excess in the disease occurrence. He named the disease haemochromatosis. Thereafter, a large contradictory debate was initiated to identify the etiology of this ‘idiopathic’ iron overload occurring out of haematological disease and iron supplementation. Some people supported the role of associated factors, such as alcohol, in its development, leading to the hypothesis of secondary iron overload linked to excessive alcohol intake. However, others supported the hypothesis of a primary iron overload disease linked to genetic factors [3,4]. Simon et al. definitively demonstrated in 1976 that the original clinical picture was related to genetic factors, linking the disease to chromosome 6, more specifically in area p21, close to HLA genes which were subsequently used for family studies for 20 years [5]. In addition, he demonstrated that the transmission of this GH was recessive. At the same time, the clinical description of GH was completed especially with the reports of patients exhibiting cardiac complications, osteoporosis and arthritis, hypogonadism and dermoskeleton alteration [6].

Understanding of the pathophysiology of the development of iron overload and its complications is a major challenge to improve the follow-up of haemochromatosis patients as well as to increase, from this ‘model disease’, our knowledge of iron metabolism.

**Normal iron metabolism**

Iron, a transition metal, is required for cell life. It is involved in a large number of biological functions, especially in oxygen transport when associated with haemoglobin, and also in the activity of a large number of enzymes, requiring iron as a cofactor and playing a role in the different metabolisms. For this purpose, iron must be present in sufficient concentrations and adequately distributed to the different cell types requiring the presence of iron [7].

The total amount of iron in the body is close to 4 g for an adult. Such a quantity of iron must be strictly controlled to ensure that the amount of iron is sufficient, to avoid manifestations linked to iron deficiency, and not excessive to limit its potential toxicity. The control of iron stores and distribution involves a large number of genes encoding proteins, thus ensuring iron metabolism homeostasis. Mutations in some of these genes may promote the development of genetic iron overload [8]. We will briefly describe iron metabolism before the presentation of GH pathophysiology.

Plasma plays a major role in iron metabolism. Indeed, despite the fact that plasma iron concentration is low (12–25 μM), this iron form is the only one available for cells. Therefore, the control of plasma iron is a major goal. The main sources of iron for plasma are macrophages and enterocytes. The control of iron import in plasma from these cells involves hepcidin.

Macrophages are involved in recycling iron from erythrocytes [7]. Indeed, erythrocytes concentrate 70% of the body iron for incorporation into haemoglobin. When erythrocytes reach their lifespan, they undergo the erythrophagocytic process within macrophages. Haem is then extracted from erythrocytes and iron is released under the haem oxygenase action. Iron can therefore be stored in macrophages within ferritin – the iron-storage protein which may contain up to 4500 iron atoms under a chemically inactive form – or released in plasma through the ferroportin protein. Ferroportin is a protein encoded by the SLC40A1 gene and located in the cell membrane [9,10]. It transfers ferrous atoms of iron (Fe²⁺) from the macrophage cytoplasm towards plasma. In addition, iron must be oxidized to Fe³⁺ (the ferric form of iron) to be taken in charge by transferrin, the plasma iron transport protein. Each molecule of transferrin may link two atoms of iron. Ceruloplasmin, a multicopper oxidase synthesised by the liver, ensures this oxidase activity [11]. A transferrin saturation coefficient,
corresponding to the ratio of plasma iron concentration versus total plasma transferrin concentration, can be calculated (normal range values 30–45%). The quantity of iron released daily by macrophages is close to 20 mg and ensures the maintenance of the plasma iron level throughout the day.

Enterocytes also play a role in the maintenance of iron concentration in plasma and therefore of iron stores. Indeed, every day, there are nonregulated and incompressible losses of iron, especially through cell desquamation, urine, feces and menses in women [7]. Therefore, iron must be extracted from nutrients and absorbed to compensate for its losses. In addition, pregnancy and growth phases require more iron. Iron absorption takes place in the duodenum at the apical pole of enterocytes, through mechanisms involving specific transporters [12]. Iron is then either addressed to ferritin and stored within the enterocyte, or directed towards the basolateral pole of the enterocyte. When stored in the enterocyte, iron is not absorbed due to enterocyte desquamation into digestive lumen. When addressed to basolateral pole of enterocyte, atoms of iron are in a position to be released in plasma, through the ferroportin protein [9,10]. Like in macrophages, an oxidation phase occurs thereafter to ensure the association of iron to transferrin. This is performed by hephastin, a glycosylphosphatidylinositol (GPI) -anchored protein with ferroxidase activity [13].

Hepcidin is a peptide of 25 amino acids in its mature form, synthesised by hepatocytes and secreted in plasma [14–17]. It targets the ferroportin protein which is especially located in macrophages and enterocytes. When interacting with ferroportin, hepcidin promotes its internalisation and then its degradation through the proteasome. Therefore, the hepcidin level, by limiting ferroportin expression at the cell membrane, controls the iron leakage into plasma and modulates both plasma iron and transferrin saturation levels. The plasma hepcidin level is regulated by various stimuli. Thus, secondary iron excess induces hepcidin expression through a molecular cascade involving the Bone Morphogenetic Protein 6 (BMP6) produced by iron-loaded hepatocytes and interacting at the cell membrane with a complex associating a specific BMP receptor [18,19], composed of two subunits, and haemojuvelin as a co-receptor. Then, phosphorylated BMP receptors induce a phosphorylation of cytoplasmic SMAD 1/5/8 proteins which then interact with SMAD4. The SMAD1/5/8/4 complex is translocated to the nucleus and interacts with a specific BMP-responsive element in the hepcidin promoter, thus inducing transcription of the hepcidin mRNA [20]. The increase of plasma hepcidin concentration limits ferroportin expression at the cell membrane and therefore decreases the plasma iron levels to counteract the iron excess.

Other genes also play a role in the signal transduction related to iron: the HFE gene product is expressed at the cell membrane in association with the beta2 microglobulin and favours the signal linked to BMP6 [21]; the gene TFR2, coding the transferrin receptor 2, also plays a role in the iron-related regulation of hepcidin expression [22]. Despite the demonstration of the positive role of these two genes in the control of hepcidin expression, precise mechanisms are not fully characterised. Inflammation also strongly promotes hepcidin expression, especially due to the increase of interleukin-6 levels which stimulate, through the cell receptor, the STAT3 pathway and therefore the transcription of the hepcidin gene, thanks to a specific binding site for phosphorylated form of STAT3 in the hepcidin promoter [23–25]. During inflammation, such abnormally high hepcidin levels regarding the iron stores promote iron retention in macrophages and limit iron absorption. This plays a role in the development of anaemia related to chronic diseases. Conversely, hepcidin levels are decreased by hypoxia and anaemia. Mechanisms could involve i) the hypoxia transcription factor hypoxia-inducible transcription factor (HIF) [26] and ii) a soluble signal linked to the increase of erythropoietic activity required to compensate hypoxia. The role of growth developmental factor 15 (GDF15) has been evoked [27].

Pathophysiology of iron overload in GH

The original description of GH corresponds to the disease related to the homozygous p.Cys282Tyr mutation in HFE gene which represents more than 95% of GH. However, other causes of GH have been described more recently. Most of the cases of GH are related to an inappropriately low hepcidin level leading to increased iron leakage from macrophages and enterocytes and then to an increase of plasma iron and transferrin saturation. Other types of GHSs are linked to ferroportin gene mutations.
Hepcidin deficiency
Hepcidin deficiency has been described in haemochromatosis linked to mutations in hepcidin, haemojuvelin, HFE or transferrin receptor 2 genes [28,29]. This leads to a plasma iron increase favouring the appearance of non-transferrin-bound iron (NTBI) which plays an important role in the development of iron overload [30].

Genes involved in hepcidin deficiency. It is obvious that homozygous or compound heterozygote mutations in the coding sequence of the hepcidin gene itself strongly inhibit hepcidin expression, therefore leading to extremely severe GH with juvenile expression. Fortunately, such mutations are exceptional [31]. It is noteworthy that some mutations in the 5'-untranslated region of the mRNA or in the hepcidin promoter may have an impact on hepcidin expression [32,33].

Mutations (homozygous or compound heterozygote) in the haemojuvelin gene are very rare and also induce a juvenile form of GH [34]. This impact is related to the major role of haemojuvelin protein in the transduction of BMP6-related signaling in hepcidin expression regulation [35].

The homozygous p.Cys282Tyr (C282Y) mutations of the HFE gene also favor the development of a situation of abnormally low hepcidin levels, leading to the development of iron overload [36]. This mutation is found at the heterozygous state in 10% of the Caucasian population, and 3 per 1000 are homozygous and therefore exposed to the risk of iron overload development. The mutation alters the signal transduction linked to BMP6 [21]. However, the penetrance of the disease is quite variable [29,37], ranging from an absence of bioclinical expression to severe organ damage compromising life expectancy. This suggests that other environmental or genetic factors could play a role in the pene-
trance of the disease. It is noteworthy that the p.His63Asp (H63D) polymorphism alone, present in 30% of Caucasians, does not induce the development of iron overload. Other rare deleterious mutations or deletions have been reported [38,39].

Homozygous or compound heterozygous mutations in the TFR2 gene also induce low levels of hepcidin by mechanisms not yet fully understood. It is noteworthy that some cases of the disease have been recorded in younger patients compared to HFE-related haemochromatosis [40].

Role of NTBI in the development of iron overload. When transferrin saturation increases, NTBI may appear in plasma [30,41,42]. In normal situations, plasma iron is linked to transferrin, a protein secreted by hepatocytes, which ensures iron delivery to cells. Mechanisms of uptake implicate transferrin receptor 1, a cell membrane protein linking transferrin and allowing its endocytosis. This mechanism is controlled by the iron regulatory protein (IRP)/iron-responsive element (IRE) couple. In a condition of cell iron excess, the cytoplasmic IRPs do not further interact with the IREs which are nucleotidic sequences localised in the 3'-untranslated region of the transferrin mRNA. This allows degradation of transferrin mRNA and then limits transferrin iron uptake in condition of cellular iron excess [43]. NTBI uptake is not downregulated in such situations [44,45]. Therefore, iron continues to enter the cell despite iron overload. NTBI being especially uptaken by liver, pancreas and heart, this explains why it plays a key role in the development of iron overload.

Ferroportin disease
Ferroportin is the target of hepcidin, and mutations in the SLC40A1 gene also induce GH [46]. It is noteworthy that the transmission of the disease is dominant. The mutation may have two different impacts which correspond to a loss or a gain of function.

Loss of function is the most frequent consequence of the mutation [47,39]. In this case, the mutation limits either the expression of the protein at the cell membrane or its capacity to export iron to plasma. Therefore, iron egress is limited especially from macrophages which are overloaded. This explains that the phenotype of the disease is characterised by plasma iron and transferrin saturation which are either normal or decreased. Hepatocytes may also present some degree of iron overload which could be related to the fact that some of them express low levels of ferroportin [48] or to another unknown mechanism, NTBI being undetectable in those patients. In addition, despite the decrease of ferroportin function, digestive iron absorption is not abolished, suggesting that other mechanisms involved in iron uptake may exist.
Gain of function applies to a few cases. The ferroportin gene mutation leads to structural changes with impossibility for hepcidin to interact with ferroportin which keeps its iron export capacity. Then, the disease is characterised by a phenotypic presentation similar to hepcidin deficiency with increase of plasma iron and transferrin saturation.

**Diagnosis and phenotypic classification**

Iron overload is suspected in two situations: in the presence of clinical symptoms (knowing that many of them are non-specific), and, most often, when plasma transferrin saturation is increased (in theory >45%, but in practice often >60% in men and >50% in women) or plasma ferritin is >300 µg L⁻¹ in men and >200 µg L⁻¹ in women.

Clinical symptoms suggestive of GH are: chronic asthenia, arthralgia, arthritis, chondrocalcinosis, skin pigmentation, hepatomegaly, unexplained liver disease, type 1 diabetes, osteopenia or osteoporosis, and cardiac symptoms (rhythm disturbances, cardiac failure).

For HFE-related haemochromatosis (type 1 haemochromatosis), the diagnosis is based on the association of increased transferrin saturation (TS) and the p.Cys282Tyr mutation in a homozygous state.

However, clinicians have to diagnose non-HFE haemochromatosis and rule out hyperferritinemia not related to haemochromatosis by checking for the main causes of non-haemochromatosis ferritin increase such as alcohol, inflammation, cell necrosis or dysmetabolic iron overload syndrome. A decision tree is proposed in Fig. 1 adapted from [49], based on suggestive symptoms and signs and/or hyperferritinemia.

Briefly, if TS is >45%, HFE testing is performed to find C282Y homozygous patients or, more rarely, compound heterozygote patients C282Y/H63D who have a much lower chance of developing iron overload.

**Fig. 1.** Algorithm for the diagnosis of genetic causes of hyperferritinemia (adapted from [49]). TS: transferrin saturation; HIC: hepatic iron concentration.
overload in the absence of other environmental factors. When no mutations for HFE are found, non-HFE haemochromatosis is to be considered (type 2, 3 and 4B).

If TS is <45% and hyperferritinemia not related to haemochromatosis is ruled out, liver iron content has to be evaluated by magnetic resonance imaging (MRI) or biopsy. In the case of hepatic iron concentration (HIC) increase, ferroportin disease or hereditary aceruloplasminemia can be considered; if HIC is normal, the hyperferritin-cataract syndrome has to be investigated.

A phenotypic five-scale grading has been proposed [50] to summarise the impact of the disease (Fig. 2) and to make a decision for treatment. Stage 0: genetic predisposition (genotype) without any clinical phenotype; stage 1: stage 0 + isolated increased transferrin saturation (>45%); stage 2: increase in both transferrin saturation and serum ferritin (>200 μg l⁻¹ in women and >300 μg l⁻¹ in men): this is the cut-off for treatment; stage 3: decrease of quality of life due to asthenia and/or arthropathy; and stage 4: life-threatening symptoms such as liver cirrhosis, diabetes, cardiomyopathy and hepatocellular carcinoma.

The French National Health Authorities (Haute Autorité de Santé (HAS)) published recommendations (with an English version) for assessment of patients with type 1 haemochromatosis according to the phenotypic scale (http://www.has-sante.fr/portail/upload/docs/application/pdf/hemochromatosis_guidelines_2006_09_12__9_10_9_659.pdf).

Stage 0 and 1. No tests are required, but a careful physical examination looking for asthenia, melanodermia, arthralgia and familial haemochromatosis is necessary. Ferritin and TS should be assessed every 3–5 years or in the case of new clinical signs.

Stages 2, 3 and 4. In addition to serum iron overload assessment and physical examination, four organs are targeted:

- Liver: Transaminases, liver ultrasound in the case of clinical hepatomegaly or transaminase increase. In the case of transaminase increase, hepatomegaly or ferritin above 1000 μg l⁻¹ a liver

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Fig. 2. Haemochromatosis phenotypic grading scale for severity of the disease (adapted from [50]). TS: Transferrin Saturation; SF: Serum Ferritin. *fatigue, arthropathy, **cirrhosis, hepatocellular carcinoma, diabetes, heart failure.
biopsy is indicated. This is not for the diagnosis of haemochromatosis which is made on both serum iron parameters and genotyping, but to detect liver fibrosis and especially cirrhosis.

- **Gonads:** Hypogonadism is assessed in males, clinically and biologically with testosterone dosage.
- **Bone:** Dual X-ray absorptiometry (DXA) is indicated to diagnose osteopenia or osteoporosis in the case of osteoporosis cofactors such as hypogonadism in males and osteoporosis in females or cirrhosis.
- **Heart:** An echocardiography is required.

### Different types of hereditary haemochromatosis

**Type 1 haemochromatosis [29]**

This is by far the most frequent form of haemochromatosis. It concerns Caucasians and especially Celtic populations. It is due to the p.Cys282Tyr (C282Y) mutation of the HFE gene, located on chromosome 6. Homozygosity is the condition for developing the disease, even if the clinical penetrance is far from being 100%. Compound heterozygosity C282Y/H63D does not lead to clinical iron overload [34]. One woman in one hundred and 25% of men with C282Y homozygosity have a phenotype of iron overload [51]. This means that other genetic and environmental factors are needed to develop the disease and are susceptible to modify the disease expression. Combinations with mutations in HAMP or HJV genes are rare. BMP2 variants have been found to increase the penetrance of C282Y homozygosity. However, these situations are rare [39]. Alcohol abuse, transfusions, dysmetabolic hepatosiderosis or chronic iron supplementation may represent environmental factors.

**Type 2 haemochromatosis [31,34]**

It is also known as ‘juvenile haemochromatosis’. Mutations on two different genes can be involved. The type 2A haemochromatosis is related to mutations in the hemjuvelin gene (HJV) located on chromosome 1. Type 2B haemochromatosis is characterised by hepcidin gene (HAMP) mutations. This leads to an early and massive iron overload with predominant heart and endocrine damages. Fortunately, this type remains exceptional.

**Type 3 haemochromatosis [52]**

It is a rare form of haemochromatosis related to mutations of transferrin receptor 2 (TFR2). Phenotypic expression resembles that of type 1 haemochromatosis.

**Type 4 haemochromatosis [46]**

It is more frequent than type 2 and 3 haemochromatosis. It is also called ‘ferroportin disease’ and is related to mutations in the ferroportin gene (SCL40A1) on chromosome 2. It is the only type of haemochromatosis transmitted in an autosomal dominant way. The 4 A type is due to mutations on the SCL40A1 gene resulting in a loss of function and haemochromatosis with iron overload in the reticuloendothelial system: spleen macrophages and Kupffer cells with normal or low plasma iron and transferrin saturation. The 4 B type makes the ferroportin resistant to hepcidin which results in a gain of function leading to a permanent release of iron in the plasma. Recent data suggest a preeminent role of sex and environmental or acquired factors in the phenotypic expression of the disease [53].

**Joint symptoms in hemochromatosis**

Joint pain is very frequent in hemochromatosis. Two-thirds of patients complain of joint symptoms which represent a major cause of impaired quality of life; in one-third of cases hemochromatosis is revealed by articular pain [51,54]. Diagnosis could be difficult when the context of iron overload is not
known. Indeed, because rheumatological symptoms are not clinically specific to haemochromatosis, the picture can mimic some frequent pathologies such as osteoarthritis, chondrocalcinosis or calcium pyrophosphate deposition (CPPD) disease. It can result in monoarthritis or polyarthritis and the axial skeleton can be involved. Pain crisis can have a degenerative or inflammatory profile. In some cases, joint deformities may direct the physician firstly to a rheumatoid arthritis diagnosis. For physicians, it is important to pick up some peculiarities of haemochromatosis arthritis, both clinically and radiologically.

Clinical presentation of hemochromatosis arthritis

Haemochromatosis arthritis is very similar to CPPD and osteoarthritis. Therefore, it is important to determine when it must be considered.

Firstly and very importantly, patients are younger than in the primitive forms of both diseases. Symptoms can begin before 30 years of age in men (or even earlier in the juvenile forms unrelated to HFE), but usually after the menopause in women. In a recent series of 199 patients, the average age of patients with their first joint symptoms was 45.8 ± 13.2 years, with a delayed diagnosis of 9 ± 10.7 years [55]. Some locations are very classic, such as the second and third metacarpophalangeal (MCP) joints causing the classic sign of ‘pain at the handshake’. The symptoms usually differ from those of inflammatory arthritis affecting the MCP joints and particularly rheumatoid arthritis. There is usually neither pain at night nor extended morning stiffness. Pain is linked to motion with stiffness limiting flexion, and a gradual onset of slightly inflammatory swelling. The wrists are often affected as well as proximal interphalangeal joints. Involvement of the hips, knees and ankles is common. Less frequently, the shoulders, elbows and spine are concerned [56,57].

Joint involvement in haemochromatosis is far from being minor. Several studies report a high number of prosthetic replacement joints compared to the general population. In one study, the risk was multiplied by 9 (confidence interval = 4.6–17.4, \( p = 8.71 \times 10^{-11} \)) in patients with haemochromatosis (\( n = 199 \)) compared to a control cohort of patients adjusted for age, sex, menopause, diabetes, C-reactive protein or body mass index and free of haemochromatosis (\( n = 824 \)). A prosthesis had been fitted in 16.1% of patients with haemochromatosis at a mean age of 58.3 ± 10.4 years, with 43.8% of them having two prostheses and 9.4% three. The most common location was by far the hip (84.6%) followed by the knee (11.5%) and ankle (3.8%). Prosthetic replacement was earlier in the case of haemochromatosis among subjects operated on: 21.9% versus 1.7% before the age of 50 years (\( p = 0.0027 \)) and 50% versus 8.6% before the age of 60 years (\( p = 8.9 \times 10^{-6} \)) [58]. This finding was confirmed in a case–control study conducted by self-administered questionnaire from haemochromatosis patients belonging to an association of patients (\( n = 306 \)) and controls (\( n = 304 \)). After adjusting for age, sex and body mass index, patients reported more hip (11.1% vs. 2.3%; odds ratio = 5.2 (2.2–11.9), \( p = 0.0001 \)) and knee replacements (3.3% vs. 0.7%; odds ratio = 5.3 (1.1–25.6), \( p = 0.03 \)) than in the control population [59].

Radiological presentation of haemochromatosis arthritis

Radiological semiology of hemochromatosis arthritis is close to CPPD. Very recently, the European League against Rheumatism (EULAR) established guidelines on CPPD. haemochromatosis was clearly identified as a cause of this affection. It was stated that haemochromatosis had to be assessed in the case of CPPD or chondrocalcinosis [60].

The most characteristic sign of haemochromatosis arthritis is the specific location on the MCP joints 2 and 3. The hook-shaped osteophyte of the metacarpal head is a very characteristic sign of haemochromatosis (Fig. 3); very often, there is a joint space narrowing of the MCP joint associated. Wrist and distal radioulnar joints are frequently affected, whereas similarly to MCP joints, these joints are usually unaffected in primary osteoarthritis. Isolated narrowing of the scaphoidtrapezium joint, without thumb osteoarthritis, is also suggestive of CPPD or haemochromatosis. Sometimes, chondrocalcinosis can be observed. Subchondral sclerosis with cysts in the chaplet is also suggestive of the diagnosis (Fig. 4). In some cases, it is not possible to differentiate between osteoarthritis and haemochromatosis arthropathy. Some locations are suggestive of haemochromatosis, especially for MCP joints, wrists,
elbows, ankles or shoulders (centred glenohumeral osteoarthritis) (Fig. 5). Sometimes, haemochromatosis leads to erosive arthritis which can mimic rheumatoid arthritis.

Recently, a radiographic score has been proposed to standardise studies. Radiographs of the hands, knees and ankles were scored for joint space narrowing, erosions, osteophytes and chondrocalcinosis. Moreover, the severity of the arthropathy was graded from 0 to 3. This is clearly a step forward for further studies of haemochromatosis arthritis. However, there are some problems of reproducibility for some items and some joints [61].

Haemochromatosis arthritis pathophysiology

The question raised is as follows: is there a direct role of iron in the genesis of arthropathy in haemochromatosis?

The link has never been clearly established; however, many arguments go in this direction. Clinical studies suggest a link between iron overload and joint damage. Ferritin levels in serum have been found correlated to the number and the severity of subchondral arthropathy [54]. In another study, there was an increase of joint disease in a group of patients with ‘probable or definite’ haemochromatosis versus patients with ‘possible or probable’ disease. There was a correlation between a serum ferritin level >1000 μg l⁻¹ and the rheumatological condition [62]. A previous series found a link between MCP arthropathy and the degree of iron overload [63].

Considering this hypothesis, it is surprising that phlebotomies, in contrast with the visceral locations of the disease, in many cases do not have any favourable impact on this rheumatism [64]. In the article by from Sahinsegovic et al., only 13.6% of the patients had an improvement of their joint symptoms after desaturation [55]. A small series of 18 patients showed that patients with phlebotomies had a paradoxical increase of CTXII, a marker of cartilage degradation, suggesting an impact of iron removal on cartilage metabolism [65]. The only study which reported an improvement of joint pain of 46% in 62% of patients with haemochromatosis after venesections was a retrospective survey without direct physical examination [66].

In osteoarthritis, ferritin levels in synovial fluid were increased in patients with heterozygous C282Y or H63D mutation compared to patients without this mutation even though serum ferritin levels were similar in the two groups. Synovial iron sequestration was suggested to explain the lack of
improvement of joint symptoms with iron removal. However, it is not known if the same results are obtained with homozygous C282Y patients [67].

The synovial histology is similar to that in osteoarthritis [68] with more macrophages and neutrophil granulocytes, as it is found in rheumatoid arthritis, especially in patients with major deposits of hemosiderin [69]. It could be speculated that iron, found in chondrocytes, stimulates cartilage catabolic enzymes leading to joint impairment. Patients with juvenile haemochromatosis and massive iron overload have haemochromatosis arthritis; this supports the role of iron in the arthropathy pathogenesis [57].

Other hypotheses have been considered: inhibition of pyrophosphatases by iron leading to chondrocalcinosis; a PTH 44–68 fragment increase; or an association between genotype and IL1RN levels in patients with haemochromatosis and joint pain [54,56,70,71]. The HFE protein is similar to that of other major histocompatibility complex class-1 proteins; C282Y HFE mutation is associated with abnormal expression of MHC class I molecules and an impaired class I antigen presentation pathway [72].
Bone loss in GH

Clinical aspects of osteoporosis in haemochromatosis

Bone involvement in GH is classical [73]. It was first described in 1960 in France by Delbarre et al. [74] Unfortunately, it was initially attributed to alcoholism or hypogonadism, two conditions leading to osteoporosis and frequently associated with haemochromatosis. However, these assumptions are no longer valid. Currently, diagnosis of haemochromatosis is made very early, very often at stage 2 of the disease, without visceral complications, and nevertheless osteoporosis is not rare, even though hypogonadism itself has become rare: 6% in males and 5% in females [75]. Moreover, the genotype can rule out the sole responsibility of putative alcoholism in bone loss. In recent series with hemochromatosis genotyping and bone assessment with DXA (dual X-ray absorptiometry), which is the standard technique for osteoporosis assessment, the prevalence of osteoporosis (T score < −2.5) was comprised between 25.3% and 34.2% [76–78]. Fracture frequency is less well known. It has been estimated at 20% of patients in an old study, before the HFE gene was discovered [79]. There are no series collecting data on systematically peripheral fractures and vertebral fractures which require, for the latter, systematic spine X-rays. Indeed, two-thirds of osteoporotic vertebral fractures have few or no clinical symptoms to the extent that patients do not consult their doctor. However, fractures are sometimes the way to diagnose haemochromatosis [80,81]. Osteoporosis has been described in juvenile haemochromatosis [82]. Despite this, apart from in France (see Diagnosis and Phenotypic Classification), international guidelines for haemochromatosis do not include osteoporosis assessment [49,83].

Pathophysiology of bone loss in haemochromatosis

More recent studies in this field show that osteoporosis associated with haemochromatosis is not due to hyperparathyroidism, vitamin D deficiency, hypogonadism or liver failure even if they can be responsible for secondary osteoporosis [54,76–78]. Therefore, it is possible that iron has a direct toxicity on bone metabolism [84]. Human studies have shown a negative correlation between HIC and bone mineral density (BMD) at the femoral neck, and between serum ferritin or the quantity of removed iron and lumbar BMD. Changes in bone turnover markers are not very informative [77,78]. There are few data on human bone biopsies. Usually, they come from old studies and are biased because of the lack of genotype, the presence of hypogonadism, cirrhosis or alcoholism. They showed an increase in bone resorption area and a decrease in osteoid thickness, which means an increase in osteoclasts (bone resorption) and a decrease in osteoblast (bone formation) activity [85,86].

In minipigs with exogenous iron overload, there was a decrease in bone formation without any change in bone resorption [87]. In vitro models showed the same decrease in osteoblast function [88,89]. Conversely, other models showed a global increase in bone remodeling in rats [90]. In HFE knockout mice, there was a phenotype of bone loss, with iron found in bone trabeculae with Perl’s staining, and a significant increase in osteoclasts and not in osteoblast number [91]. In vitro, iron is capable of inhibiting bone crystal growth with significant changes in crystallinity and carbonate substitution [92].

Management of haemochromatosis

Venesection therapy [50]

There are two phases: an induction phase and a maintenance phase. Guidelines have been developed for type 1 haemochromatosis. However, they can apply to type 2, 3 and 4B.

During the induction phase, phlebotomies are performed weekly: 7 ml kg⁻¹ without exceeding 550 ml per session. The serum ferritin level is measured monthly until values move below 300 μg l⁻¹ in males and 200 μg l⁻¹ in females; then bi-monthly until the goal of ferritin ≤50 μg l⁻¹ is achieved. The haemoglobin level should always be above 11 g dl⁻¹. The goal of the maintenance phase is to keep ferritin level ≤50 μg l⁻¹. Usually, one phlebotomy every 2–4 months is sufficient. Ferritin is checked after every two phlebotomies.
For type 4A haemochromatosis (ferroportin disease), there is a risk of anaemia during the treatment. It should be monitored very carefully with regular hemoglobin assessment. A ferritin level higher than 50 \( \mu \text{g} \text{L}^{-1} \) can be accepted (MRI is valuable to quantify residual tissue iron excess).

In the absence of a physiological iron removal mechanism, phlebotomies are performed lifelong. Venesections are contra-indicated definitively in the case of sideroblastic anaemia or other causes of central anaemia, thalassemia major and severe cardiopathy not linked to haemochromatosis. They are temporarily contra-indicated in the case of: anaemia due to iron insufficiency <11 g dl\(^{-1}\), low blood pressure <100 mmHg, lower limb arteriopathy, stroke, heart beat <50 bpm or >100 bpm, pregnancy, insufficient venous network and an impaired general condition.

**Family screening**

For HFE haemochromatosis, the physician has to give information to the patient (= the proband) about the consequences of the disease for him(her)self and for his (her) family.

Because of the potential severity of the disease and the opportunity of initiating preventive treatment, it is advised that the patient informs his (her) family members that they should be tested. The modalities depend on the country and the health insurance system. However, only adults have to be tested (because no treatment is considered in children). Transferrin saturation, serum ferritin and HFE genotype are recommended in siblings and children of the patient. In parents, the genotype is needed only in the case of an increase in blood iron parameters. Another solution for children is to test the other parent. If there is no HFE mutation, children cannot be homozygous for the C282Y mutation.

**Haemochromatosis arthritis**

X-rays are needed for symptomatic joints. There is no evidence-based treatment for haemochromatosis arthritis. Unfortunately, phlebotomies are most often non-effective \[39,64\]. Treatment is then the same as for osteoarthritis and CPPD. In our practice, analgesics are regularly efficient. Non-steroidal anti-inflammatory drugs are useful temporarily in the case of an acute flare. Colchicine at low doses (0.5–1 mg daily) could also be used.

Intra-articular glucocorticosteroids (at best guided with arthrography or ultrasound) are usually very effective.

In some patients there is destructive arthritis, which is severely disabling. No disease-modifying anti-rheumatic drugs (DMARDs) used in inflammatory rheumatisms, such as rheumatoid arthritis, have been studied in this indication. However, by analogy with disabling forms of CPPD, according to recent EULAR recommendations, hydroxychloroquine could be an option in very inflammatory joint diseases more so than methotrexate because of its potential liver toxicity. IL1 blockers may be promising but further studies are needed \[93\].

**Osteoporosis**

DXA is needed in patients with previous low energy fractures, severe iron overload, hypogonadism or classical osteoporosis fracture risks.

As for haemochromatosis rheumatism, there is no evidence-based medicine for treatment in this particular situation. It is not known if venesections improve BMD and decrease risk fracture. There are very little data on this subject. In one female, BMD had improved after phlebotomies \[94\], but not in males without a treatment for hypogonadism \[82,95\].

Guidelines for post-menopausal and male osteoporosis apply for osteoporosis in haemochromatosis. Patients with osteoporotic fractures or with low BMD or osteopenia with other risk factors for fracture need to be treated with approved osteoporosis medications in their country. Minimal management for osteoporosis is based on: regular physical activity, dietary calcium intake of about 1 g daily (or if impossible by water rich in calcium or a calcium drug), obtaining a 25 OH vitamin D serum level of 30 ng ml\(^{-1}\) and stopping bone toxins such as alcohol.
Summary

In conclusion, GH is a hereditary disease expressed by iron overload in tissues. In Caucasians, it is most often due to homozygosity of the C282Y HFE gene mutation, but other genes may be involved. In the absence of treatment by venesections, patients can develop life-threatening visceral damage such as liver cirrhosis and carcinoma, diabetes or heart failure. Phlebotomy treatment has been remarkably successful in preventing these complications, but patients survive with other symptoms of the disease susceptible to impair, sometimes seriously, their quality of life. This is the case of arthropathy and osteoporosis complicating haemochromatosis. In the wake of discoveries made in recent years in the knowledge of iron metabolism, significant advances have been made in the understanding of the joint and bone damage in this disease. However, there is a need for specific therapeutic strategies for bones and joints in these patients. In any case, it confers an important role on rheumatologists, together with hepatologists and hematologists, in the diagnosis and management of GH.

Practice points

- In the case of unexplained joint pain or arthropathy resembling osteoarthritis, chondrocalcinosis or CPPD, haemochromatosis should be suspected, especially in people younger than in the usual presentation of these diseases or in case of unusual joint location.
- Haemochromatosis arthropathy is associated with a higher rate of joint prosthesis replacement than in the general population and in younger people.
- Osteoporosis is a complication of iron overload and haemochromatosis. It should be assessed particularly in patients with severe overload and other risk factors for osteoporosis or with previous low energy fractures.

Research agenda for basic and clinical research

- Clinical and basic studies on hemochromatosis arthropathy are needed to determine the physiological mechanisms of this complication and above all to find treatments for improving the quality of life of the patients.
- Clinical and basic studies on hemochromatosis osteoporosis are needed. We do not know precisely the fracture incidence in this disease. We do not know if venesections have an effect on the outcome of osteoporosis or which treatment for osteoporosis may be better. Finally, findings on bone loss in iron overload could be helpful for post-menopausal osteoporosis.

Acknowledgements

The authors would like to thank Association Fer et foie; Fédération Française des Associations de Malades de l’Hémochromatose (FFAMH); European Grant Euro-Iron (LSH-CT-2006-037296); Société Française de Rhumatologie (SFR); Région Bretagne. The authors also thank Vicki McNulty for her help in preparing the manuscript.

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