Arthropathy of genetic hemochromatosis:
A major and distinctive manifestation of the disease

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ABSTRACT
Genetic hemochromatosis is not a rare disease and represents a frequently underestimated cause of arthropathy. Joint involvement is one of the most frequent manifestations of the disease and presents typical clinical and radiological features that strongly suggest the diagnosis. Joint complaints are often the first clinical manifestation of GH. Their identification may be crucial to establish the diagnosis in the pre-cirrhotic phase and to institute appropriate therapy to prevent organ damage and associated mortality. Recent identification of the genetic defect responsible for the disease is leading to new insights into the pathogenesis of GH and the associated arthropathy.

Introduction

Classic genetic hemochromatosis (GH) is an iron storage disease with a recessive autosomal genetic transmission. It results from the inappropriately high intestinal absorption of iron and the subsequent deposition of this metal in several organs, eventually resulting in organ lesions and functional insufficiency. Classically, GH is characterized by the triad of liver cirrhosis, diabetes mellitus and skin hyperpigmentation. Arthropathy was recognized as a manifestation of GH only in 1964 (1), almost one hundred years after the first descriptions of the condition. Nevertheless, it is one of the most common manifestations of the disease and the most detrimental to the patient's quality of life. The arthropathy of GH presents several characteristic clinical and radiological features which strongly suggest the diagnosis.

Genetic hemochromatosis
Epidemiology
GH is one of the most common genetic anomalies among the Caucasian population, in whom more than 0.3% are homozygous and 10% are heterozygous for the disease (2). GH is characterized by excessive iron deposition in parenchymatous cells, especially in the liver, pancreas and heart. Accumulated iron is held to be responsible for the cellular lesions, although the exact mechanisms involved remain unknown.

Duodenal iron absorption is augmented in excess of 4 times the normal rate. Clinical expression of the disease is 5 to 10 times more frequent in males than in females, probably due to the protective effect of iron loss associated with menstrual menses and pregnancy. The first symptoms develop in almost 70% of patients between the ages of 40 and 60 years (2).

Pathogenesis
In 1996, Feder described the HFE gene, which has been demonstrated to be responsible for the majority of cases of GH in the Caucasian population (3). This gene is incorporated in the class I major histocompatibility complex (MHC I), and localizes very close to HLA-A. The HFE protein is expressed on the cell surface, where it associates to the transferrin receptor, reducing its affinity by 5 to 10 times and thus decreasing the amount of transferrin that enters the cell (4). In the European population, between 60-100% of all patients with GH are homozygous for a punctual mutation in this gene, consisting of a substitution of cystein in position 282 by tirosin (C282Y) (5). As a result of this mutation, there is no expression of HFE on the cell surface, the transferrin receptor is not inhibited and an excessive amount of transferrin enters the cell (6).

Another mutation of HFE, the H63D mutation, has been described as common in the general population. On its own, this mutation does not seem to determine iron loading. However, compound heterozygote patients (C282Y and H63D) may develop considerable iron storage and even clinical hemochromatosis (7). Furthermore, several

studies of linkage disequilibrium suggest that the ability of the C282Y mutation to induce iron loading can be modulated by a number of other genes, yet to be identified (8). These additional genetic factors may contribute to the variability of the disease's clinical expression.

The integration of the HFE gene within MHC I suggests a link between the immune system and iron metabolism. In fact, there is evidence that patients with GH may present several immunological abnormalities. A considerable proportion present abnormally low numbers of CD8+ T lymphocytes and raised CD4:CD8 ratios. These changes are related to a higher accumulation of iron (9, 10). The CD4:CD8 ratio has even been proposed as a good indicator of the clinical course of the disease (9). It is interesting to note that these changes in peripheral lymphocytes remain unchanged after efficient treatment of the disease, suggesting that they are not a consequence of iron overloading (9).

It has also been demonstrated that a mouse strain which does not express MHC I antigens, and therefore does not have CD8+ lymphocytes, spontaneously develops iron overload on hepatocytes and, in addition, presents changes in iron hemostasis similar to those found in human GH (11, 12). Several functional abnormalities on CD8+ lymphocytes have been described in patients with GH, and these are positively correlated with the development of liver cirrosis (13-15). These observations support the hypothesis that the immunological changes associated with GH may actually modulate iron deposition and the clinical expression of the disease.

Clinical aspects
The clinical manifestations of GH include skin hyperpigmentation, diabetes mellitus, liver and heart dysfunction, arthropathy and hypogonadism. Liver involvement may initially show up only in the form of hepatomegaly or moderate changes in liver enzymes. With time, however, the condition progresses to liver dysfunction and cirrhosis. Hepatocellular carcinoma becomes a complication in about 30% of patients

with liver cirrhosis (2). Skin hyperpigmentation is due to the deposition of melanin and is usually generalized. Heart involvement results in heart failure and arrhythmias. Hypogonadism is due to low levels of gonodotropins, resulting from an iron overload in the hypophysis. Osteoporosis has been described in 25 to 50% of cases, usually associated with hypogonadism (16). The association of the typical clinical manifestations suggests the diagnosis. However, numerous patients do not present the classical triad of hepatomegaly, diabetes and hyperpigmentation. In fact, in a review of 93 patients, only 8% presented the classical triad at the time of diagnosis (17).

The phenotypical expression of GH is highly variable, depending on the organs involved in each patient and the severity of the dysfunction. While some patients develop a particularly severe form of the disease with multiple organ failure, some homozygous subjects may never develop clinical disease (2, 18).

The combined determination of serum ferritin and transferrin saturation remains the most simple and reliable screening method for GH (19), even in the asymptomatic phase. In homozygous patients, transferrin saturation is elevated quite early in life - usually higher than 50% in females and 60% in males. Serum ferritin is a good indicator of the total body iron load and is generally quite elevated. A definite diagnosis can be established in two different ways: (1) genetic typing (although not all patients present the known HFE mutations), and (2) liver biopsy, which allows a definite diagnosis if iron overloaded hepatocytes can be demonstrated, with a liver iron index higher than 1.9. Liver biopsy has the additional advantage of allowing evaluation of tissue damage. The iron index is calculated by dividing the concentration of iron in the dried liver fragment (expressed in micrograms/ 100 ml) by age.

Treatment is based on the removal of excessive iron through phlebotomies and symptomatic management of any organ dysfunction. Each 500 ml phlebotomy contains 200 to 250 mg of iron.

They are repeated, once a week at the start, until the saturation of transferrin and serum ferritin fall below 50% and 50 g/l, respectively. Even then, it is indispensable to repeat the phlebotomies as needed, usually every 3 months, in order to avoid the re-accumulation of iron (2).

The main causes of death in the absence of treatment are heart failure, liver cirrhosis and hepatocellular carcinoma. Life expectancy for symptomatic patients receiving adequate treatment is in the range of 90% at 5 years. The removal of excessive iron can ameliorate the liver, heart and pancreatic lesions and prevent hepatocellular carcinoma, but has no effect upon hypogonadism or arthropathy once these are established. Early diagnosis is, therefore, essential and screening of the patient's relatives is mandatory (2).

The arthropathy of genetic hemochromatosis

Clinical aspects
Hemochromatosis arthropathy tends to start at the small joints of the hands, with special emphasis on the second and third MCP joints. The first symptoms are arthralgias emerging after prolonged exercise, progressive stiffness and restriction of MCP flexion. With time, the deformity of these joints becomes apparent and the arthropathy extends to involve the proximal interphalangeals and wrists as well (Fig. 1). In many patients, joint involvement becomes more widespread, extending to the elbows, shoulders, hips, knees, ankles and the spine, not rarely resulting in considerable disability requiring intensive rehabilitation and surgery.

At the other extreme of the clinical spectrum, patients may have only moderate arthralgia, predominantly at night and early in the morning (20-24). In some cases, episodes of acute synovitis may occur, probably due to the deposition of calcium pyrophosphate dihydrate crystals (pseudogout) (25). On clinical grounds, the arthropathy of hemochromatosis may therefore be mistaken for osteoarthritis, primary calcium pyrophosphate dihydrate (CPPD) deposition arthropathy or even rheumatoid arthritis (26).

Fig. 1. Hands of a 63-year-old patient with genetic hemochromatosis (GH). Note the prominent swelling of the second and third MCP joints.

Radiology

On radiological examination, GH arthropathy may superficially resemble osteoarthritis, based on the common features of joint space loss, subchondral cysts, sclerosis and osteophytosis. Some typical aspects may also suggest primary CPPD disease, given that the two conditions share several characteristics: (1) involvement of joints usually spared by osteoarthritis, such as the MCP, wrists, elbows and shoulders; (2) the presence of large subchondral cysts; (3) uniform loss of joint space, contrary to the asymmetrical distribution of this feature in osteoarthritis; and (4) the frequent association of chondrocalcinosis, which may involve the knees, wrists, pubic sinfisis, intervertebral discs, shoulders and hips (27).

Despite this, GH arthropathy presents several radiological features that may be considered as characteristic or even specific (27), thus allowing the differential diagnosis from CPPD:

- preferential involvement of the MCP joints, especially the second and third, with more pronounced joint space loss which may also involve the fourth and fifth MCP (Fig. 2);
- very typical, hook-shaped osteophytes, in particular emerging from the radial sides of the metacarpal distal epiphisis (Fig. 3). Similar osteophytes may also be observed in other affected joints, such as the elbows, shoulders and hips;
- diffuse involvement of the wrist but with a lower prevalence of scapholunar dissociation and radiocarpal involvement; and
- in the hip it is occasionally possible to identify a radiolucent zone in the subchondral area of the femoral head, a finding that has been considered to be specific for GH arthropathy (23-25, 27-29).

However, most patients with GH arthropathy do not present the typical features described above, making the disease indistinguishable, if based solely on clinical and radiological grounds, from CPPD or even osteoarthritis (30, 31). In addition, a metacarpophalangeal arthropathy similar to GH has been described in some patients with type II diabetes mellitus and has also been associated with intense manual work (32, 33) (Fig. 4).

Pathogenesis

The pathogenesis of GH arthropathy remains unknown. It is very tempting to assume that iron overload is responsible for the joint disease. In fact, excessive iron deposits have been demonstrated in the synovial membrane of patients with this condition (34). Iron salts have been shown to promote the nucleation of calcium pyrophosphate crystals and inhibit its removal from the joints (35-37), thus supporting a role for iron in the development of chondrocalcinosis and pseudogout. However, the iron deposits and calcium pyrophosphate crystals found in the synovium of GH patients are not spatially related (38). Furthermore, no hemossiderin has been found in the fibrocartilage and hyaline cartilage of these patients.

It is important to recognize that many patients with GH do not develop joint disease and that, in those who do, there is no correlation between the extent of the iron deposits and the radiological and pathological findings in the joints (24). Furthermore, GH treatment does not ameliorate the joint disease. Addi-

Fig. 2. Postero-anterior radiograph of the hands of the same patient with GH.

Fig. 3. Close-up of the same patient's right hand, showing hook-shaped osteophytes on the second and third metacarpal heads.

tional arguments against a primary pathogenetic role for iron is given by the observation that excessive iron deposits in the synovium are also found in rheumatoid arthritis, osteoarthritis, pigmented villonodular synovitis, hemophilia, hemarthrosis and acquired hemocromatosis, although the joint involvement in these conditions is quite dissimilar to that seen in GH (24, 39-41). Interestingly, juvenile GH, which is not associated with the HFE gene mutation, does not present arthropathy. All of these observations strongly suggest that other factors besides iron deposition may be responsible for the arthropathy associated with adult GH.

One possibility is that joint involvement derives from a different metabolic defect, which accompanies but is independent from iron metabolism. A disturbance of parathyroid hormone (PTH), consisting in the elevation of the serum concentration of PTH fragments, has been suggested to play a role, but studies on this subject have not yielded conclusive results (42).

Another possibility is that the development of the arthropathy depends on the presence of genes that modify or modulate the clinical expression of the C282Y mutation in HFE (8).

It has also been suggested that the immunological abnormalities associated with GH may be responsible for the development of arthropathy in some patients, in the same way as they seem to modulate the degree of iron overload and susceptibility to liver cirrhosis (9-15).

Prevalence of arthropathy in genetic hemochromatosis

Arthropathy is one of the most common manifestations of GH, affecting 28 to 81% of all patients, depending on the study (17, 25, 30, 31, 42-45). Furthermore, 31 to 60% of all patients with GH present an arthropathy with typical radiological features, particularly in the MCPs (17, 25, 30, 31, 42). The prevalence of chondrocalcinosis is lower, as it is present in 3.8 to 38% of patients (17, 30, 31, 42). Episodes of acute synovitis (pseudogout) seem to be relatively rare (22, 31, 44).

The average age of patients with arthropathy at diagnosis is in most series higher than the age of those without joint involvement. On the other hand, arthralgias are the most frequent and the longest lasting manifestations of the disease (17, 31). This is in clear contrast with the previous clinical concept of GH which underestimated arthropathy, and underlines the need to consider the possibility of this disease when faced with a compatible pattern of joint involvement.

Presently, GH is frequently detected and treated in the early phases of the disease, making it rare to have the classical clinical triad (17). In addition, as progression of arthropathy is not modified by treatment, joint involvement will become an even more important aspect of genetic hemochromatosis.

This arthropathy may be extremely disabling, and frequently requires joint prosthesis (46). Adams *et al.* evaluated the impact of the diverse clinical manifestations of GH on the quality of life of 50 patients and concluded that arthropathy has the largest functional impact, although cirrhosis is the most im-

Fig. 4. Radiograph of the hands of a 68-year-old patient. The radiological features of the MCPs are similar to GH arthropathy, but the patient does not have hemochromatosis or diabetes mellitus. He worked in a profession that required heavy manual labour.

portant factor in mortality (47).

In conclusion, GH arthropathy presents typical clinical and radiological features that should suggest the diagnosis, represents one of the most frequent manifestations of the disease and has a major functional impact on the quality of life. Its pathogenesis may not be directly related to iron overload, but may be linked with metabolic and immunological abnormalities induced by the HFE gene mutation or associated genes. Arthropathy is frequently the first clinical manifestation of GH, allowing the diagnosis to be established in the pre-cirrhotic phase and therefore allowing the prevention of organ involvement and associated mortality.

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