The Hand Arthropathy of Hereditary Hemochromatosis Is Strongly Associated with Iron Overload

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ABSTRACT. ***Objective***. To analyze the clinical characteristics and genetic background associated with the presence of hand arthropathy, as determined by radiological findings, in Italian patients with hereditary hemochromatosis (HHC).

Methods. In 88 consecutive unselected patients with phenotypically expressed HHC, joint involvement was systematically evaluated in plain radiographs of hands, wrists, lumbar spine, pelvis, and knees. Risk factors considered were age, sex, body mass index, alcohol abuse, organ involvement at other sites, and indices of iron overload, including ferritin, transferrin saturation, and iron removed to reach depletion. *HFE* genotype was also considered. The independent role of risk factors was tested by logistic regression analysis.

Results. Thirty-two subjects (36%) showed signs of metacarpophalangeal (MCP) arthropathy. Intercarpal, radiocarpal, and chondrocalcinosis were less frequent and occurred in association with MCP arthropathy. At multivariate analysis MCP arthropathy was independently associated with older age [odds ratio (OR) 1.20, 95% confidence interval (CI) 1.1–1.33/yr; p = 0.0001], higher ferritin levels at diagnosis (OR 4.17, 95% CI 1.60–13.9 for values > 1000 ng/ml; p = 0.008), the presence of the C282Y +/+ and C282Y/H63D HFE genotypes (OR 2.69, 95% CI 1.09–7.87; p = 0.04), and higher percentage transferrin saturation (OR 1.05, 95% CI 1–1.1; p = 0.05). The severity of arthropathy was independently associated with older age (p = 0.03) and higher ferritin values (p = 0.05).

Conclusion. MCP arthropathy together with a typical pattern of joint involvement is observed in one-third of unselected patients with HHC, and is influenced by the duration and degree of the iron overload. (First Release Dec 1 2007; J Rheumatol 2008;35:153–8)

Key Indexing Terms:
HFE PROTEIN HEMOCHROMATOSIS IRON OSTEOARTHRITIS

Hereditary hemochromatosis (HHC) is a common inherited disorder with a prevalence of about 1 in 300, characterized by increased intestinal iron absorption and progressive accumulation in parenchymal tissues, with subsequent organ malfunction. The liver, pancreas, heart, and pituitary are frequently involved[1]. Homozygosity for the C282Y mutations of the *HFE* gene involved in iron sensing is responsible for the majority of HHC cases[2], but geographical differences have been reported and the prevalence of *HFE*-unrelated HHC is about 30% in Southern Europe[3].

An association between HHC and arthritis, first described in 1964[4], has been reported in 13%–80% of cases, depending on the diagnostic criteria[5-7]. The arthropathy of HHC displays typical clinical and radiological features, such as preferential involvement of the metacarpophalangeal (MCP) joints, especially the second and third, with hook-shaped osteophytes on the radial sides of the metacarpal epiphysis, roughened and irregular joint surfaces, severe narrowing of the articular space, and presence of subchondral cysts. It is also characterized by wrist involvement, and, occasionally, radiolucency in the subchondral area of the femoral head and chondrocalcinosis[8].

A direct pathogenic role for synovial iron overload has been proposed[9], but evidence is controversial[10]. The interaction between *HFE* and other genetic determinants and secondary hormonal changes[11] have been suggested to play a role.

HHC treatment by iron depletion does not ameliorate established joint disease, and, although cirrhosis is the major factor determining survival, arthritis is the prominent clinical factor affecting the quality of life[12]. Moreover, heterozygosity for *HFE* mutations has been proposed as a genetic determinant for a specific subtype of polyarticular osteoarthritis, char-

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Supported by COFIN 2004, FIRST 2004, FIRST 2005, Ricerca Corrente Ospedale Maggiore Policlinico Mangiagalli Regina Elena IRCCS 2004, 2005, 2006.

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Accepted for publication September 10, 2007.

acterized by MCP, elbow, and ankle involvement, in the general population[13,14]. Based on these findings, it is evident how the identification of determinants of the specific arthropathy could have wide diagnostic and potentially therapeutic implications.

We previously reported in a small group of patients with HHC an 81% prevalence of radiological specific and unspecific arthropathy, which, in agreement with findings by other groups[5], was associated with older age[15]. However, the relatively low number of patients included in the studies published to date did not allow analysis of the determinants of the specific hand arthropathy in unselected patients with HHC. Thus, it is possible that the reported results are biased by the coexistence of unspecific osteoarthritis (OA), recognizing different pathogenic factors, and by the lack of statistical power.

Our aim was to analyze the clinical characteristics and genetic background associated with the presence of specific hand arthropathy, as determined by radiological findings, in a series of 88 Italian patients with HHC.

MATERIALS AND METHODS

We considered 88 consecutive unselected patients with phenotypically expressed HHC diagnosed between 1992 and 2003 at the Department of Internal Medicine, who agreed to be referred to the Rheumatology Unit (G. Pini Hospital, Milano), as part of a screening strategy for the detection of extrahepatic organ involvement in patients with HHC. Only 2 patients who presented symptomatic arthropathy were first seen at the Rheumatology Unit. Part of this group has been described[15]. Demographic features and clinical information on organ involvement were available for each included subject. The presence of alcohol abuse (> 60 g/day for more than 5 yrs) and chronic viral hepatitis (HbsAg or HCV-RNA positivity) was also recorded. The diagnosis of hemochromatosis was made on the basis of increased ferritin (> 320/240 ng/ml for males and females, respectively) and transferrin saturation (> 50%/45% for men and women, respectively) in the presence of homozygosity for the C282Y or compound heterozygosity for the C282Y and H63D *HFE* mutations. In the absence of these *HFE* genotypes, a liver biopsy showing moderate to severe parenchymal iron overload or hepatic iron index (hepatic iron concentration/age) > 2, and an amount of iron removed by phlebotomy > 5/3.5 g for men/women in the absence of secondary causes of iron overload, were required for the diagnosis.

Iron measurements at diagnosis and the amount of iron removed to reach depletion[16] were not available in 6 subjects who had started iron depletion before presentation to our centers, and *HFE* gene mutations were not available in 5 subjects who died or were lost to followup after 1996[2]. One patient was compound-heterozygous for the C282Y HFE mutation and the E302K hemojuvelin mutation. One patient had 1q-linked juvenile hemochromatosis related to hemojuvelin mutations. Liver biopsy was performed in 74 subjects because of serum ferritin > 1000 ng/ml and age > 40 years, or increased transaminases or diagnosis confirmation, as advised by widely accepted guidelines[1]. Hepatic siderosis was graded according to Scheuer, *et al*[17]. Liver iron concentration was assessed in 26 subjects for whom a sufficient amount of tissue was available according to Barry and Sherlock[18]. The *HFE* genotype was determined by restriction analysis[19]. Mutations in hemojuvelin, hepcidin, transferrin receptor-2, and ferroportin 1 were excluded by denaturing high performance liquid chromatography and sequencing in subjects with HFE genotypes different from C282Y +/+ and C282Y/H63D.

Radiographs of the lumbar spine, hands, wrists, knees, and pelvis were obtained from all patients and evaluated by the same expert radiologist, who was unaware of clinical diagnosis and blinded to all clinical, biochemical, and genetic features of the patients. Hand arthropathy was evaluated according to Kallman, *et al*[20]. Briefly, individual joints were assessed for the presence of osteophytes (graded from 0 to 3), joint space narrowing (0–3), subchondral sclerosis (0–1), subchondral cysts (0–1), lateral deformity (0–1), and collapse of central joint cortical bone (0–1). Patients were diagnosed as having specific MCP arthropathy when Kallman score evaluated at the level of second and third MCP joints was ≥ 1 bilaterally. Arthropathy at other sites was diagnosed when radiographic changes were present showing at least narrowing of a joint space or prominent osteophytosis in one or more joints, according to the method of Kellgren and Lawrence[21]. Free testosterone and parathyroid hormone (PTH) levels at diagnosis were available for subjects evaluated after 1994. Demographic, genetic, and clinical features of the included subjects and the reasons for referral to our center are shown in Table 1.

Informed written consent was obtained from each patient, and the protocol was approved by the institutional review boards of the Policlinico and G. Pini Hospitals.

Statistical analysis. Results are shown as mean ± SD, except for serum ferritin and PTH levels. Due to non-normal distribution, the geometric mean and interquartile range are shown for the latter variables, and results were compared after log-transformation. Fisher's exact test and Student's t-test were used for comparisons of frequencies and means, correlations were performed by the Pearson's test. To adjust the risk of unspecific arthropathy associated with MCP arthropathy for confounding factors, we performed logistic regression analyses considering MCP arthropathy as dependent variable, and age (yrs), sex, body mass index (BMI; kg/m^2), and joint involvement at a specific site as independent variables. We estimated adjusted odds ratios (OR) for specific arthropathy by logistic regression analysis, considering as independent variables those significant at univariate analysis and the genetic status

Table 1. Clinical and genetic features of 88 patients with hereditary hemochromatosis.

Feature	Mean ± SD / n (%)
Age	48.6 ± 11.5
Male sex (%)	71 (81)
HFE gene status (%)†	
C282Y/C282Y	52 (63)
C282Y/H63D	6 (7)
C282Y/wt and H63D/H63D	5 (6)
H63D/wt and wt/wt	20 (24)
Cause of referral (%)	
Altered biochemical values	67 (76)
Family screening	15 (17)
Clinical manifestations††	18 (20)
Organ involvement (%)	
Cirrhosis	30 (34)
Diabetes	13 (15)
Hypogonadism	28 (32)
Hyperpigmentation	11 (13)
Cardiopathy	6 (7)
Osteoporosis	22 (25)
Ferritin (ng/ml)*, median (interquartile range)	1000 (652–2422)
Transferrin saturation (%)*	77 ± 20.6
Iron removed (g)*	8.98 ± 7.3
Liver iron concentration (μg/100 mg dry tissue)**	1200 ± 730
Hepatic iron index**	4.9 ± 3.28
Hepatic siderosis (%)***	
Grade I–II	37 (50)
Grade III–IV	37 (50)

† Available for 83 subjects regularly followed after 1996. †† In 2 patients HHC was diagnosed following evaluation at the Rheumatology Unit for arthritis symptoms. * Available for 84 subjects presenting at our center before starting iron depletion; ** available for 26 subjects; *** available for 74 subjects submitted to liver biopsy. Siderosis was graded according to Scheuer[17]. wt: wild-type.

(presence or not of a genotype consistent with classic HHC). Given the non-normal distribution, we used the median value as threshold for serum ferritin. Differences were considered significant when p was < 0.05 (2-tailed). The severity of specific joint involvement was evaluated as the bilateral sum of Kallman OA grade at the second and third MCP joints, which was approximated to a continuous variable. The independent predictors of the severity of MCP arthropathy were evaluated by multiple regression analysis including variables significant at univariate analysis.

RESULTS

Thirty-two subjects (36%) showed signs of specific hand arthropathy (Table 2). In 2 cases arthropathy was the presenting symptom leading to the diagnosis of HHC, which was made at 48 and 45 years, 5 and 4 years after symptoms onset, respectively. Both patients were homozygous for the C282Y *HFE* mutation and had ferritin levels higher than 1000 ng/ml at diagnosis of HHC.

Forty-nine subjects (56%) were affected by unspecific polyarticular OA. The prevalence of joint disease at other sites typically involved in HHC was lower and tended to occur in association with MCP arthropathy. Ten patients (8%, all with MCP arthropathy; p < 0.0001 for association with MCP arthropathy) were affected by trapezioscaphoid arthropathy, 3 (3%, all with MCP arthropathy; p = 0.04 for association with MCP arthropathy) by radiocarpal arthropathy, and 2 (2%, all with MCP arthropathy; p = 0.05 for association with MCP arthropathy) by specific hip arthropathy (subchondral radiolucency). Ankle involvement was not specifically evaluated in these subjects.

The prevalence of interphalangeal hand OA [19 (59%) vs 11 (20%); p = 0.0002 for association with MCP arthropathy], hip OA [16 (50%) vs 15 (27%); p = 0.03], and wrist OA [8 (25%) vs 1 (2%); p = 0.001) was also significantly higher in patients with than in those without specific hand arthropathy. No significant difference was observed in the prevalence of knee OA [13 (41%) vs 12 (21%); p = 0.08] and spine OA [18 (57%) vs 22 (39%); p = 0.18]. In patients with MCP arthropathy, there was a higher risk of observing unspecific hand OA (OR 2.04, 95% CI 1.2–3.6, p = 0.01) and wrist OA (OR 4.35, 95% CI 1.7–19, p = 0.01), but not of hip OA (OR 1.25, 95% CI 0.7–2, p = 0.4), independently of age, sex, and BMI.

Among the variables considered, the number of affected joint sites was significantly correlated with age ($R^2 = 0.35$; p < 0.0001), ferritin ($R^2 = 0.15$; p = 0.0004), and the amount of iron removed to depletion ($R^2 = 0.10$; p = 0.002).

Clinical and biochemical features associated with the presence of specific second and third MCP joint arthropathy are shown in Table 3. Specific hand arthropathy was associated with older age, more severe indices of iron overload (ferritin and transferrin saturation at diagnosis, iron removed to reach depletion), and the presence of cirrhosis, and there was a trend for an association with diabetes. No significant difference in BMI values, prevalence of alcohol abuse [7 (22%) vs 12 (21%)], and chronic viral hepatitis [5 (16%) vs 5 (9%)] was observed between affected and unaffected subjects. MCP arthropathy was not influenced by the year of HHC diagnosis.

The prevalence of MCP arthropathy according to *HFE* genotype is shown in Table 4. We subdivided patients in 3 groups, according to *HFE* genotypes (1) consistent with HHC (C282Y +/+ and C282Y/H63D), (2) usually associated with mild iron overload (C282Y/wild-type and H63D +/+), and (3) usually not associated with iron overload (H63D/wild-type and absence of *HFE* mutations). The prevalence of second and third MCP joint arthropathy, the sum of bilateral second and third MCP joint OA grade according to Kallman, and trapezioscaphoid arthropathy, as well as of chondrocalcinosis, were very similar irrespective of the genetic background of iron overload. The severity of iron overload, as evaluated by the amount of iron removed to depletion and ferritin and diagnosis, was not significantly different among these groups.

Table 2. Radiological joint involvement in 88 patients affected by hereditary hemochromatosis.

Joint Involvement	n (%)
Specific 2nd–3rd joint MCP arthropathy	32 (36)
Trapezioscaphoid joint arthropathy	10* (11)
Chondrocalcinosis	10* (11)
Interphalangeal arthropathy	30 (34)
Wrist arthropathy	9 (10)
Hip arthropathy	31 (35)
Knee arthropathy	25 (28)
Spine arthropathy	30 (34)
Polyarticular osteoarthritis	49† (56)

Polyarticular osteoarthritis: presence of arthropathy at at least 2 different sites. * All with MCP arthropathy (p < 0.0001 vs absence of MCP arthropathy). † 25 (78%) with and 24 (43%) without MCP arthropathy (p = 0.002 for association with MCP arthropathy). MCP: metacarpophalangeal.

Table 3. Clinical features of 88 patients with hereditary hemochromatosis subdivided according to the presence or not of specific hand arthropathy.

	MCP Arthropathy		
	Present, n = 32	Absent, n = 56	p
Age (yrs)	54.6 ± 9.6	45.1 ± 11.1	< 0.0001
Sex female	4 (12)	13 (23)	0.27
BMI (kg/m^2)	24.2 ± 2.4	24.1 ± 3.2	0.85
Ferritin (ng/ml)*, median (IQR)	1902 (837–3515)	1000 (452–1525)	0.0007
Transferrin saturation, %*	86.6 ± 15	71.7 ± 21	0.0002
Iron removed (g)*	10.8 ± 7.6	7.9 ± 6.9	0.04
Free testosterone (pg/ml)**	6.5 ± 3.9	11.3 ± 6.3	0.01
PTH (pmol/l)**, median (IQR)	3.3 (2.8–4.5)	3.3 (2.7–4.7)	0.46
ALP (IU/ml)	126.5 ± 42	112.6 ± 52	0.18
ALT (IU/ml)	80.4 ± 54	57.9 ± 45	0.06
Cirrhosis	17 (53)	13 (23)	0.006
Diabetes	8 (25)	5 (9)	0.06
Hypogonadism	13 (41)	15 (27)	0.24

* Available for 84 subjects presenting at our center before starting iron depletion; ** available for 55 subjects. BMI: body mass index, PTH: parathyroid hormone.

Table 4. Prevalence and severity of specificd HHC-related joint involvement according to *HFE* genotype status in 83 patients with hereditary hemochromatosis.

	C282Y +/+ or C282Y/H63D, n = 58	*HFE* Genotype C282Y/wt or H63D/H63D*, n = 5	H63D/wt or wt/wt**, n = 20
2nd and 3rd MCP arthropathy, n (%)	21 (36)	1 (20)	8 (40)
OA grade of 2nd and 3rd MCP joints	4.9 ± 8.4	2.6 ± 5.3	4.6 ± 8
Trapezioscaphoid arthropathy, n (%)	6 (10)	1 (20)	2 (10)
Chondrocalcinosis, n (%)	5 (8.6)	0	2 (10)
Iron removed	9.0 ± 7.8	7.0 ± 3.7	9.0 ± 6.9
Ferritin, ng/ml, median (IQR)	1000 (466–2375)	1000 (742–2800)	1600 (700–2840)

* One patient was compound heterozygous for the C282Y HFE mutation and the E302K hemojuvelin mutation, without evidence of MCP arthropathy. ** One patient had juvenile hemojuvelin-related HHC and presented MCP arthropathy. wt: wild-type.

Next, we analyzed independent predictors of second and third MCP joint arthropathy by multivariate analysis (Table 5). We included variables significant at univariate analysis and, to correct for the genetic background, the presence of *HFE* genotype consistent with HHC. MCP arthropathy was independently associated with older age (OR 1.20, 95% CI 1.1–1.33 per yr, p = 0.0001), higher ferritin levels at diagnosis (OR 4.17, 95% CI 1.60–13.9 for values > 1000 ng/ml, p = 0.008), the presence of the C282Y +/+ and C282Y/H63D HFE genotypes (OR 2.69, 95% CI 1.09–7.87, p = 0.04), and higher percentage transferrin saturation (OR 1.05, 95% CI 1–1.1, p = 0.05).

Finally, we analyzed variables associated with the severity of specific arthropathy, defined as the bilateral sum of Kallman OA grade at the second and third MCP joints. The severity of arthropathy was significantly correlated with age (R^2 = 0.05, p = 0.025), transferrin saturation (R^2 = 0.10, p = 0.004) and ferritin (R^2 = 0.15, p = 0.0003) at diagnosis, and the amount of iron removed to depletion (R^2 = 0.11, p = 0.002). At multivariate analysis, only age (p = 0.03) and ferritin (p = 0.05) were independently associated with the severity of joint involvement.

Table 5. Adjusted odds ratios for specific MCP arthropathy evaluated by logistic regression analysis in 77 patients with hereditary hemochromatosis. Logistic regression analysis considering age (yrs), presence of cirrhosis, transferrin saturation (% value), ferritin (above or below 1000 ng/ml, median value), iron removed to reach depletion (g), and presence of *HFE* genotypes consistent with HHC as independent variables.

MCP Arthropathy	OR	95% CI	p
Age at diagnosis (per 1-yr increase)	1.20	1.10–1.33	0.0001
Cirrhosis	0.71	0.28–1.68	0.43
Transferrin saturation at diagnosis (per 1% increase)	1.05	1.00–1.10	0.05
Ferritin at diagnosis (> 1000 ng/ml)	4.17	1.60–13.9	0.008
Iron removed (per 1-g increase)	0.88	0.78–0.98	0.08
HFE C282Y +/+ or C282Y/H63D	2.69	1.09–7.87	0.04

DISCUSSION

In our study, we analyzed the prevalence and determinants of the specific hand arthropathy of HHC, as determined by radiological evaluation, in unselected patients with different degrees of iron overload and genetic background. Characteristic second and third MCP joint involvement, the hallmark of HHC arthropathy, was observed in 36% of patients and was associated with iron stores and older age.

This prevalence confirms previous findings in a limited subset of patients[15], but is lower than that reported by other authors in a smaller study[5], possibly due to the inclusion in our study of all patients evaluated for HHC at the Department of Medicine, irrespective of clinical symptoms. The different clinical setting, i.e., unselected patients versus patients first evaluated at a rheumatology clinic, may also contribute to explain the low observed prevalence of chondrocalcinosis, which was 11% in our series compared to 22% to 66% in previous reports[5,22].

MCP arthropathy involving the second and third joints, the most characteristic form of joint involvement, was strongly associated with trapezioscaphoidal arthropathy and chondrocalcinosis, which always occurred in patients with MCP involvement, albeit at lower frequency. In our study, 56% of patients were classified as having polyarticular OA based on radiological findings, supporting the view that unspecific OA-like arthropathy, characterized by cartilage degeneration and subchondral bone proliferation, is also a feature of HHC. Interestingly, spine OA, observed in 45% of patients, occurred independently of specific arthropathy. By contrast, hand and wrist OA, observed in 34% and 10% of patients, respectively, were associated with specific MCP joint involvement independently from demographic and anthropometric variables. The association between MCP and hip arthropathy[23] was less strong. These data are consistent with the existence of an OA phenotype associated with iron overload characterized by the involvement of hands and wrists[13,14]. In this series, we

observed ankle arthropathy in 2 subjects with MCP disease, but the presence of ankle and elbow arthropathy was not routinely assessed.

The larger number of patients considered compared to previous studies[15] allowed us to subsequently assess factors associated with specific hand arthropathy. Previous studies demonstrated a significant relationship between older age and radiological abnormalities considered as a whole, whereas only a trend was reported for specific disease[5,15]. We demonstrated a relationship between MCP arthropathy and age, and observed an association with the severity of HHC, as evidenced by higher prevalence of cirrhosis and more severe indices of iron overload in affected patients.

Multivariate analysis showed that serum ferritin, a reliable indicator of iron stores in HHC[24,25], and transferrin saturation at diagnosis were strong predictors of specific hand arthropathy, independently of confounding variables. Moreover, ferritin values were also independently associated with the radiological severity of specific MCP joint involvement. It should be noted that the association of arthropathy with ferritin was stronger than that with the amount of iron removed to reach depletion, suggesting that ferritin also reflects iron stores that could not be mobilized by phlebotomy. On the other hand, ferritin values should only marginally be influenced by inflammation, since this is not a prominent feature of HHC arthropathy[25].

Importantly, the prevalence of MCP arthropathy was similar in patients with HHC independently of *HFE* genotype, suggesting again a direct role of iron overload in the pathogenesis of arthropathy, whatever the underlying genetic defect. However, a limitation of this analysis is the low number of non-C282Y +/+ subjects, who could recognize different underlying genetic factors with different risk of arthropathy. Nonetheless, multivariate analysis showed that the degree of iron overload at diagnosis was associated with specific arthropathy independently of *HFE* genotype. Patients with ferritin > 1000 ng/ml had a 4.2-fold higher risk of specific arthropathy, and the risk increased by 20% per each year increase of anagraphical age. No patient with age lower than 35 years and ferritin lower than 1000 ng/ml had specific arthropathy. These findings closely mirror what was observed for liver damage in HHC, which was correlated with the duration and severity of iron overload. A limitation of this study is related to the lack of histological evaluation and iron quantification of joint tissues, which precluded evaluation of the correlation between ferritin and the degree and localization of iron overload. These results suggest that early initiation of phlebotomy could possibly prevent the development of arthropathy in HHC, since established arthritis leads to progressive structural damage even after the removal of the triggering factor. This hypothesis should be evaluated further in future studies.

Specific MCP arthropathy together with a typical pattern of joint involvement is observed in roughly a third of unselected HHC patients, and is associated with severe iron stores and older age.

ACKNOWLEDGMENT

We thank Laura Cremonesi, Paolo Arosio, Giorgio Biasiotto, Maurizio Sampietro, and Dario Tavazzi for performing HFE, ferroportin-1, hemojuvelin and hepcidin genotyping.

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