Musculoskeletal Complications of Hereditary Hemochromatosis: A Case-Control Study

PASCAL RICHETTE, SÉBASTIEN OTTAVIANI, ERIC VICAUT, and THOMAS BARDIN

ABSTRACT. ***Objective.*** Arthropathy that mimics osteoarthritis (OA) and osteoporosis (OP) is considered a classic complication of hereditary hemochromatosis (HH) but has never been investigated in a cross-sectional study. We investigated whether HH is associated with increased prevalence of OA and OP and related factors.

Methods. A self-administered questionnaire was completed by 306 patients with HH and 304 age and sex-matched unaffected controls.

Results. The mean age of patients was 60.1 ± 11.3 years, and 47.4% were women. More patients with HH than controls had been given a diagnosis of OA: 50.5% vs 28.9% [adjusted OR (aOR) 2.5, 95% CI 1.8–3.6]. Compared with controls, patients with HH had a higher risk of knee (aOR 5.3, 95% CI 1.1–25.6) and hip replacement prosthesis (aOR 5.2, 95% CI 2.2-11.9). More patients than controls had been diagnosed with OP: 23.3% vs 4.6% (aOR 7.3, 95% CI 3.2–17.0). Patients with HH showed an increased prevalence, although not significant, of wrist (aOR 1.7, 95% CI 0.9-3.0) or vertebral fractures (aOR 1.7, 95% CI 0.8-3.8). The severity of iron overload, as defined by a ferritin level > 1000 μg/l at diagnosis, was associated with OA (p = 0.0005), OP (p = 0.01), presence of hip prosthesis (p = 0.04), wrist fractures (p = 0.002), and vertebral fractures (p = 0.02).

Conclusion. This case-control study strongly suggests a significant association among HH, OA, and OP. Joint involvement can be severe, especially in patients with substantially elevated ferritin levels. (J Rheumatol First Release August 1 2010; doi:10.3899/jrheum.100234)

Key Indexing Terms:
HEREDITARY HEMOCHROMATOSIS OSTEOARTHRITIS OSTEOPOROSIS
CARTILAGE PHLEBOTOMY IRON

The most common form of hereditary hemochromatosis (HH) is an autosomal recessive iron-overload disorder associated with mutation of the *HFE* gene, located on chromosome 6. Approximately 90% of subjects with HH who are of northern European descent are homozygous for a missense mutation that results in the substitution of tyrosine for cysteine at position 282 of the HFE protein (C282Y)[1]. Another mutation on the *HFE* gene can result in the substitution of aspartate for histidine at aminoacid 63 (H63D). About 5% of people with HH may show compound heterozygosity for both the C282Y and H63D mutation[1,2].

Large controlled studies showed that the penetrance of the homozygous state for the HFE C282Y mutation is much lower than had previously been thought. These studies showed that the classically nonspecific symptoms attributed to iron overload in C282Y homozygotes were equally prevalent in controls, which led to a more specific definition of penetrance based on the presence of liver disease[2,3].

Two rheumatological complications have been reported in phenotypically expressed HH: an arthropathy that mimics osteoarthritis (OA) but with a different joint distribution, and osteoporosis (OP)[4,5,6,7,8]. Schumacher was the first to describe articular complications in patients with HH[9]. Since then, numerous observational studies have reported that affected individuals frequently show arthralgia in the hands and large joints or severe arthropathy, typically involving the second and third metacarpophalangeal (MCP) joints, which may seriously affect quality of life[4,5,10,11,12,13]. This arthropathy was reported to occur in 30% to 80% of patients with HH, depending on the study[5,14], and frequently coexists with calcium pyrophosphate deposition[12]. Chondrocalcinosis may also cause severe attacks of inflammatory arthritis and may also associate with intermittent or persistent symptoms of pain, stiffness, and functional limitation[15]. The reported prevalence of OP ranges from 25% to 35%[6,8] and seems to be associated with severity of iron overload[6]. The risk of vertebral fractures has been reported to reach 20%[16].

Descriptions of articular and bone involvement in pheno-

From the Université Paris 7, UFR médicale, Assistance Publique-Hôpitaux de Paris (APHP), Hôpital Lariboisière, Fédération de Rhumatologie; Université Paris 7, UFR médicale, APHP, Hôpital Fernand-Widal, Unité de recherche clinique, Paris, France.

Supported by the "Association Rhumatisme et Travail," Hôpital Lariboisière.

P. Richette, MD, PhD; S. Ottaviani, MD; T. Bardin, MD, Université Paris 7, UFR médicale, APHP, Hôpital Lariboisière, Fédération de Rhumatologie; E. Vicaut, MD, PhD, Université Paris 7, UFR médicale, APHP, Hôpital Fernand-Widal, Unité de recherche clinique.

Address correspondence to Dr. P. Richette, Fédération de Rhumatologie, Hôpital Lariboisière, 2 Rue Ambroise Paré, 75475 Paris cedex 10, France. E-mail: pascal.richette@lrb.aphp.fr

Accepted for publication May 31, 2010.

typically expressed HH have involved highly selected subjects, mainly from rheumatological departments in tertiary care hospitals, and were mostly based on observational studies without an appropriate control group. Given that OA, joint pain, and OP are frequent conditions within the general population, data from these studies do not allow definite conclusions on the link between HH and rheumatological features.

In contrast to those descriptions in patients with phenotypically expressed HH, case-control studies that have compared joint pain or arthritis in homozygotes for the *HFE* mutation with controls yielded conflicting results. Some studies found that arthritis or presence of abnormal second and third MCP joints was more common in C282Y homozygotes than in controls[17,18]; others found that the prevalence of joint pain or arthritis was similar in C282Y homozygotes and controls[19,20,21,22,23]. Moreover, a recent metaanalysis of 66,000 cases and 226,000 controls found the hemochromatosis genotypes (C282Y/C282Y or C282/H63D) not associated with arthritis[24].

The purpose of our national survey was to specifically assess the prevalence of joint and bone involvement in patients with HH and in age-matched and sex-matched healthy controls. We also studied whether patients with substantially elevated ferritin levels at diagnosis were at risk for rheumatological complications.

MATERIALS AND METHODS

Cases and controls. Patients who were members of the Association Hémochromatose France (AHF), the French HH patient association, were asked to participate in a national survey in 2006. AHF is a nonprofit support organization with 2284 members throughout France. AHF edits a bimonthly journal that provides general information on the condition. A self-administered questionnaire was inserted into the journal in June 2006, and we invited all members to participate in our survey. A similar questionnaire was completed by a control group of healthy unrelated subjects (blood donors or volunteers recruited from 2 different university-hospital blood donor centers and from the local community, respectively). The control subjects were matched for age and sex to the patients with HH. Patients and controls were informed of the purpose of the study and gave their informed consent. This study was conducted in accord with the recommendations of the Helsinki Declaration. Ethical approval was not required for the study, in accord with national guidelines.

Method of enquiry. The self-administered questionnaire addressed articular, lumbar spine, and bone involvement. The following data were collected: demographic measurements (age, sex, weight, size, genotype, smoking habit); details of HH history (ferritin level and transferrin saturation at diagnosis, method of detection of hemochromatosis and symptoms before diagnosis); general clinical measurements (asthenia, diabetes mellitus, liver disease, cardiac disease); joint and spine involvement (patients were asked if they have been diagnosed with OA by a physician; if they complained of joint pain, low back pain, or sciatica; if they had knee, hip, or ankle replacement prosthesis); bone involvement (patients were asked if they had been diagnosed with OP by a physician; if they had a history of fractures, menopausal status, current treatment for OP, and maternal history of hip fracture); and, finally, effect of phlebotomy on global joint pain, if present, before the start of venesection therapy.

A pilot version of the questionnaire was administered to 15 patients with HH not included in the study and was modified for comprehensibility according to their remarks and suggestions.

Statistical analysis. Student's t test or chi-square test was used to compare quantitative or qualitative data, respectively. Prevalence of the clinical symptoms or events was described by crude or adjusted OR (aOR) with 95% CI. Measurements for groups were compared by logistic regression. The design of our study precluded the assessment of iron overload by liver biopsy. We thus used the ferritin level as a surrogate marker, and we defined the severity of iron overload by a ferritin level ≥ 1000 μg/l at diagnosis. This cutoff was shown to be clinically appropriate[3]. All analyses used SAS v 9.2 (SAS Institute, Cary, NC, USA). A 2-tailed p value < 0.05 was considered statistically significant.

RESULTS

Demographic characteristics. Our study consisted of 306 patients with HH who completed the questionnaire and 304 controls matched for age and sex (Table 1). The mean age of patients was 60.1 ± 11.3 years, and 47.4% were female. Among the respondents, 87% were reported to be C282Y homozygote and 13% compound C282Y/H63D heterozygote. Mean ferritin level and transferrin saturation coefficient at diagnosis were 1556 ± 1623 μg/l and 74.4% ± 19.2%, respectively.

Diagnosis of HH. When asked about the features that led to the diagnosis of HH, 62.1% of respondents stated symptoms related to HH. By contrast, 23.8% reported that their diagnosis resulted from a routine or ancillary laboratory test, and 13.7% were diagnosed by family screening. Half of the respondents (49.2%) received a diagnosis from their general practitioner and only 12% from a rheumatologist.

Joint symptoms in patients with HH. At diagnosis, more than half of the patients (51.5%) reported that they complained of joint pain and 57.9% reported asthenia (Table 2). Among respondents with joint pain attributed to HH by physicians, the mean time between the start of complaints and diagnosis of HH was 8.6 ± 8 years. One-third of these patients stated that their pain worsened following phlebotomy. Only 20% reported that their articular symptoms improved with iron removal, and 31% reported no effect. Prevalence of self-reported global joint pain and asthenia at the time of the survey was higher in the HH group than in controls (p < 0.0001; Table 2). Joint pain was reported to greatly affect

Table 1. Characteristics of patients with hereditary hemochromatosis (HH) and controls. Values are mean ± SD or percentages.

Characteristics	Patients with HH, n = 306	Controls, n = 304	p
Age, yrs	60.1 ± 11.3	59.6 ± 11.6	0.56
Women, %	47.4	42.2	0.2
Menopausal women, %	77.7	67.4	0.05
Body mass index, kg/m^2	25 ± 3.7	25 ± 3.6	0.98
Current smoker, %	12.3	16.5	0.14
Bisphosphonate use, %	9.2	1.6	< 0.0001
C282Y/C282Y, %	87	NA	NA
C282Y/H63D, %	13	NA	NA

NA: not applicable.

Table 2. Self-reported symptoms at diagnosis and at time of survey in patients with hereditary hemochromatosis (HH) and controls.

Symptoms	Patients with HH, n = 306		Controls, n = 304	p*
	At Diagnosis	At Time of Survey		
Joint pain, %	51.5	86.9	43.1	< 0.0001
Asthenia, %	57.9	79.7	31.9	< 0.0001
Diabetes, %	5.2	9.8	7.9	0.40
Liver disease, %	18.4	27.1	1.3	< 0.0001
Cardiac disease, %	10	15.8	9.2	0.01

* Symptoms in controls compared with symptoms in the HH group at time of survey.

the quality of life of patients with HH (57% of responders), followed by asthenia (33%).

Painful joint sites in patients with HH. Patients were asked to locate their current painful joints. The most common painful joint in patients with HH was the knee, then the hand, ankle, shoulder, wrist, hip, and foot. Crude and adjusted analysis revealed a significantly higher prevalence of painful joints at all individual sites in patients with HH than in controls. The aOR for self-reported pain in hand, wrist, and ankle were 17.2 (95% CI 10.3–28.9), 12.2 (95% CI 6.5–22.9), and 11.3 (95% CI 6.3–20.0), respectively (Table 3).

Osteoarthritis, joint replacement, and back pain in patients with HH. Prevalence of physician-diagnosed OA, joint replacement, self-reported back pain, and sciatica in both groups is indicated in Table 4. More patients with HH than controls were diagnosed with OA: 50.5% vs 28.9% (aOR 2.5, 95% CI 1.8–3.5). Compared with controls, patients with HH showed a higher crude and adjusted risk of knee and hip replacement prosthesis (aOR 5.3, 95% CI 1.1–25.6 and aOR 5.2, 95% CI 2.2–11.9, respectively). Prevalence of self-reported back pain and sciatica was also higher in patients with HH (aOR 3.6, 95% CI 2.5-5.0 and aOR 2.1, 95% CI 1.5–2.9). The management of physician-diagnosed OA was considered satisfying by 69% of controls but only 39% of patients with HH ($p < 0.0001$).

Osteoporosis and fractures in patients with HH. In the crude analysis, more patients than controls had been diagnosed with OP: 23.3% vs 4.6% (OR 6.2, 95% CI 3.4–11.3, $p < 0.0001$; Table 5). This diagnosis was associated with an increased crude risk of wrist fracture (OR 1.7, 95% CI

Table 3. Prevalence of self-reported joint pain for each site for patients with hereditary hemochromatosis (HH) and controls.

Joint	Patients with HH, n = 306	Controls, n = 304	Crude OR (95% CI)	Adjusted OR (95% CI)*	p
Shoulder	40.8	12.2	5.0 (3.3–7.5)	5.1 (3.4–7.8)	< 0.0001
Elbow	21.2	4.3	6.0 (3.2–11.2)	6.8 (3.6–12.8)	< 0.0001
Wrist	33.0	3.9	12.0 (6.4–22.4)	12.2 (6.5–22.9)	< 0.0001
Hand	53.9	6.3	17.6 (10.5–29.4)	17.2 (10.3–28.9)	< 0.0001
Hip	34.6	5.6	8.9 (5.2–15.4)	9.3 (5.3–16.2)	< 0.0001
Knee	58.2	17.8	6.4 (4.4–9.3)	6.3 (4.3–9.2)	< 0.0001
Ankle	36.3	4.9	11.0 (6.2–19.4)	11.3 (6.3–20.0)	< 0.0001

* Adjusted for age, sex, and body mass index. P values are for adjusted OR.

Table 4. Association between hereditary hemochromatosis (HH) and osteoarthritis, joint replacement, back pain, and sciatica.

Conditions	HH, n = 306	Controls, n = 304	Crude OR (95% CI)	Adjusted OR (95% CI)*	p
Osteoarthritis, %	50.5	28.9	2.5 (1.8–3.5)	2.5 (1.8–3.6)	< 0.0001
Knee replacement, %	3.3	0.7	5.1 (1.1–23.4)	5.3 (1.1–25.6)	0.03
Hip replacement, %	11.1	2.3	5.3 (2.3–12.1)	5.2 (2.2–11.9)	0.0001
Ankle replacement, %	1.0	0.3	3.0 (0.3–30.0)	2.9 (0.3–28.4)	0.35
Back pain, %	71.5	40.8	3.6 (2.6–5.1)	3.6 (2.5–5.0)	< 0.0001
Sciatica, %	47.2	30.0	2.1 (1.5–2.9)	2.1 (1.5–2.9)	< 0.0001

* Adjusted for age, sex, and body mass index. P values are for adjusted OR.

1.0–3.0, p = 0.04). The difference in OP prevalence between groups persisted after adjusting for confounding factors (aOR 7.3, 95% CI 3.2–17.0). In the adjusted model, HH was associated, although not significantly, with wrist or vertebral fractures (aOR 1.7, 95% CI 0.9–3.0 and aOR 1.7, 95% CI 0.8–3.8, respectively).

Association between severity of iron overload and osteoarthritis or osteoporosis. Finally, we searched for an association between severity of iron overload, as assessed by a ferritin level ≥ 1000 μg/ml at diagnosis, and OA, spine involvement, or OP (Table 6). Severity of iron overload was associated with OA (OR 2.2, 95% CI 1.4–3.6) and presence of hip prosthesis (OR 2.1, 95% CI 1.0–4.4), but not knee or ankle prosthesis. No association was found with back pain or sciatica.

OP was found associated with HH and severe iron overload (OR 1.9, 95% CI 1.1–3.3) and with wrist and vertebral fractures (OR 3.0, 95% CI 1.4–6.2 and OR 2.8, 95% CI 1.1–7.0, respectively) but not hip fracture.

DISCUSSION

This is the first large case-control survey of the prevalence of rheumatological diseases classically associated with HH. Physician-diagnosed OA and OP, low back pain, and hip and knee prosthesis were all associated with HH.

Our study included 306 cases, with mean age 60.1 years. The proportions of homozygotes (C282Y/C282Y) and compound heterozygotes (C282Y/H63D) were 87% and 13%, respectively, similar to proportions reported in 2 large observational studies that specifically assessed articular complications of HH[11,12].

The increased ease of diagnosis of HH since the discovery of the *HFE* gene in 1996 has modified the phenotype of diagnosed cases[17]. Indeed, the classic triad of cirrhosis, bronze skin, and diabetes is now rare in adult-onset HH[25]. We found that circumstances leading to the diagnosis included symptoms (62.1%) and an abnormal laboratory test result (23.8%). The proportion of patients diagnosed after family screening (13.7%) was lower than that found in 2 large surveys (20% and 31%)[18,21]. About half of our patients reported joint pain before diagnosis. Despite this, only 12% received a diagnosis from a rheumatologist, and the mean delay between the beginning of joint complaints and the diagnosis of HH was 8.6 years. These data suggest that physicians, including rheumatologists, understand HH poorly. Rheumatologists should be better educated about the prevalence of HH and the methods available for diagnosis to improve care of patients with HH, because early diagnosis is associated with better outcome[1,25]. Moreover, as in previous reports[4,10,14,21,26], we found joint pain rarely alleviated by phlebotomy treatment, which highlights the need for early detection of HH in patients with articular complaints, before severe structural damage occurs.

The 2 most commonly reported painful articular sites were the knee and the hand, and any joint could be involved in HH, which agrees with a previous survey involving the US Hemochromatosis Research Foundation[14] and with radi-

Table 5. Association between hereditary hemochromatosis (HH) and osteoporosis and fractures.

Conditions	HH, n = 306	Controls, n = 304	Crude OR (95% CI)	Adjusted OR (95% CI)*	p
Osteoporosis, %	23.3	4.6	6.2 (3.4–11.3)	7.3 (3.2–17.0)	0.01
Hip fracture, %	2.6	2	1.3 (0.5–3.9)	0.8 (0.2–2.5)	0.65
Wrist fracture, %	12.4	7.6	1.7 (1.0–3.0)	1.7 (0.9–3.0)	0.08
Vertebral fracture, %	7.2	3.6	2.1 (1.0–4.3)	1.7 (0.8–3.8)	0.18

* Adjusted for age, sex, body mass index, use of bisphosphonate, smoking, menopausal status, and history of maternal fracture of the hip. P values are for adjusted OR.

Table 6. Association between serum ferritin level at diagnosis and rheumatological complications in patients with hereditary hemochromatosis (HH). n = 306.

Complications	Serum Ferritin < 1000 μg/l	Serum Ferritin ≥ 1000 μg/l	OR (95% CI)	p
Osteoarthritis, %	41.3	61.6	2.2 (1.4–3.6)	0.0005
Knee replacement, %	1.8	5.1	2.9 (0.7–11.5)	0.12
Hip replacement, %	7.7	15.2	2.1 (1.0–4.4)	0.04
Back pain, %	74.9	67.4	0.6 (0.4–1.1)	0.15
Sciatica, %	49.1	44.9	0.8 (0.5–1.3)	0.46
Osteoporosis, %	18	29.7	1.9 (1.1–3.3)	0.01
Hip fracture, %	1.8	3.6	2.0 (0.4–8.8)	0.32
Wrist fracture, %	7.1	18.8	3.0 (1.4–6.2)	0.002
Vertebral fracture, %	4.2	10.9	2.8 (1.1–7.0)	0.02

ological findings from a recent observational study[11]. Thus, joint involvement may be widespread in HH, and HH should always be considered in patients diagnosed with polyarticular OA or peripheral arthritis[27]. Given this frequent diffuse articular involvement, it is surprising that spine involvement did not receive much attention in clinical studies of HH. Disc degeneration and calcifications in the intervertebral discs due to calcium pyrophosphate crystal deposits have been reported in patients with HH[28,29], and the prevalence of spine arthropathy seen on radiography was 34% in a retrospective study[11]. The literature contains no data on the prevalence of low back pain in patients with a clinical phenotype of HH. One survey found sole carriage of the HFE gene mutation not associated with self-reported prevalence of low back pain[19], which might be explained by the low penetrance of the condition. We found a higher self-reported prevalence of low back pain and sciatica in patients than in controls, which shows that the lumbar spine might be impaired during HH.

Because the arthropathy of HH mimics OA in most cases, we assessed the prevalence of physician-diagnosed OA in patients and controls. We found this prevalence was 2.5-fold higher in patients with HH than in controls after adjusting for confounders. To estimate the severity of this arthropathy, we evaluated the prevalence of joint prosthesis of the lower limbs in both groups, and found the proportion of patients with hip and knee prosthesis about 5-fold higher at both sites than in controls. Moreover, joint pain, rarely improved by iron depletion (20%), was the prominent clinical factor affecting quality of life in patients. These data strongly suggest that the arthropathy of HH can be a severe and disabling condition.

In vitro and experimental studies have suggested that iron overload might lead to a decrease in bone formation secondary to inhibition of osteoblast activity[16,30,31], and that iron is capable of inhibiting hydroxyapatite crystal growth[32]. Increased bone resorption might also occur in the presence of hypogonadism, which is a rare complication in HH[33]. Prevalence of OP and osteopenia, as assessed by dual-energy x-ray absorptiometry, has been reported in patient series, but again, without an appropriate group control[6,8,13]. In the largest series, of 59 unselected patients (C282Y/C282Y or C282Y/H63D), prevalence of OP as assessed by bone mineral density was 20% at the lumbar spine and 12% at the femoral neck[6], which are close to the 23.3% we found. In our survey, the prevalence of physician-diagnosed OP reported by patients was 6.2-fold higher than that reported by controls, which strongly suggests that OP is a complication of HH. Whether OP is associated with increased risk of fracture in patients with HH has never been specifically addressed. In a population-based study of 501 people with HH, the incidence rate of all fractures was not significantly higher in the HH group than in the general population[17]. We found increased aOR for wrist and vertebral fractures, but these were not significantly associated with HH, which might be due to an insufficient number of patients to detect these rare events.

Recently, C282Y homozygotes with serum ferritin level ≥ 1000 μg/l were found to be at higher risk for symptoms and diseases associated with the *HFE* gene, such as fatigue, liver disease, and use of arthritis medication, than were homozygotes with a lower level of ferritin[18]. We thus searched for an association between severity of iron overload, defined by ferritin level ≥ 1000 μg/l at diagnosis, and presence of joint and bone complications. Patients with severe iron overload were at high risk for physician-diagnosed OA and OP, hip prosthesis, and wrist and vertebral fractures. These findings confirm and extend the observation from previous studies of an association between degree of iron overload and severity of arthropathy and OP[6,11,12].

Our study has several limitations that deserve attention, and some results need to be interpreted cautiously. Indeed, due to the relatively low number of respondents, participants may not have been representative of all patients with HH. For example, patients with joint pain, OA, or OP more likely responded to the survey. Patients were asked to remember symptoms and experiences attributed to hemochromatosis, and recall bias may have occurred. Moreover, physicians who are aware of rheumatological complications of HH would have been more likely to search for OP and OA in patients with HH. Finally, our control group may have been unrepresentative, because blood donors could be healthier than the general population.

This is the first case-control study that strongly suggests a significant association between HH and OA, low back pain, and OP. Joint involvement in patients can be a severe condition, especially with serum ferritin levels ≥ 1000 μg/l at diagnosis. Our findings also suggest that rheumatological complications are frequent in patients with HH and that rheumatologists should be better aware of HH to achieve an earlier diagnosis.

ACKNOWLEDGMENT

We thank all the patients who participated in this survey. We are grateful to the "Association Hémochromatose France," in particular Pr. H. Michel, who helped with data collection for patients with HH. We thank Drs. A. Leduc (Hospital Lariboisière, Paris) and C. Mesnil (Hospital Bichat, Paris), who helped with data collection for the control group. We also thank the Association Rhumatisme et Travail (Centre Viggo Petersen, Hospital Lariboisière, Paris), which funded copy editing (Laura Heraty) of this report.

REFERENCES

1. Adams PC, Barton JC. Haemochromatosis. Lancet 2007;370:1855-60.
2. Olynyk JK, Trinder D, Ramm GA, Britton RS, Bacon BR. Hereditary hemochromatosis in the post-HFE era. Hepatology 2008;48:991-1001.
3. Waalen J, Felitti VJ, Gelbart T, Beutler E. Screening for hemochromatosis by measuring ferritin levels: a more effective approach. Blood 2008;111:3373-6.

4. Schumacher HR Jr. Haemochromatosis. Baillieres Best Pract Res Clin Rheumatol 2000;14:277-84.
5. Ines LS, da Silva JA, Malcata AB, Porto AL. Arthropathy of genetic hemochromatosis: a major and distinctive manifestation of the disease. Clin Exp Rheumatol 2001;19:98-102.
6. Valenti L, Varenna M, Fracanzani AL, Rossi V, Fargion S, Sinigaglia L. Association between iron overload and osteoporosis in patients with hereditary hemochromatosis. Osteoporos Int 2009;20:549-55.
7. Jordan JM. Arthritis in hemochromatosis or iron storage disease. Curr Opin Rheumatol 2004;16:62-6.
8. Guggenbuhl P, Deugnier Y, Boisdet JF, Rolland Y, Perdriger A, Pawlotsky Y, et al. Bone mineral density in men with genetic hemochromatosis and HFE gene mutation. Osteoporos Int 2005;16:1809-14.
9. Schumacher HR Jr. Hemochromatosis and arthritis. Arthritis Rheum 1964;26:41-50.
10. Adams PC, Speechley M. The effect of arthritis on the quality of life in hereditary hemochromatosis. J Rheumatol 1996;23:707-10.
11. Valenti L, Fracanzani AL, Rossi V, Rampini C, Pulixi E, Varenna M, et al. The hand arthropathy of hereditary hemochromatosis is strongly associated with iron overload. J Rheumatol 2008;35:153-8.
12. Pawlotsky Y, Le Dantec P, Moirand R, Guggenbuhl P, Jouanolle AM, Catheline M, et al. Elevated parathyroid hormone 44-68 and osteoarticular changes in patients with genetic hemochromatosis. Arthritis Rheum 1999;42:799-806.
13. Sinigaglia L, Fargion S, Fracanzani AL, Binelli L, Battafarano N, Varenna M, et al. Bone and joint involvement in genetic hemochromatosis: role of cirrhosis and iron overload. J Rheumatol 1997;24:1809-13.
14. Schumacher HR, Straka PC, Krikker MA, Dudley AT. The arthropathy of hemochromatosis. Recent studies. Ann NY Acad Sci 1988;526:224-33.
15. Announ N, Guerne PA. Treating difficult crystal pyrophosphate dihydrate deposition disease. Curr Rheumatol Rep 2008;10:228-34.
16. Diamond T, Stiel D, Posen S. Osteoporosis in hemochromatosis: iron excess, gonadal deficiency, or other factors? Ann Intern Med 1989;110:430-6.
17. Crooks CJ, West J, Solaymani-Dodaran M, Card TR. The epidemiology of haemochromatosis: a population-based study. Aliment Pharmacol Ther 2009;29:183-92.
18. Allen KJ, Gurrin LC, Constantine CC, Osborne NJ, Delatycki MB, Nicoll AJ, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. N Engl J Med 2008;358:221-30.
19. Sherrington CA, Knuiman MW, Divitini ML, Bartholomew HC, Cullen DJ, Olynyk JK. Population-based study of the relationship between mutations in the hemochromatosis (HFE) gene and arthritis. J Gastroenterol Hepatol 2006;21:595-8.
20. Waalen J, Felitti V, Gelbart T, Ho NJ, Beutler E. Prevalence of hemochromatosis-related symptoms among individuals with mutations in the HFE gene. Mayo Clin Proc 2002;77:522-30.
21. McDonnell SM, Preston BL, Jewell SA, Barton JC, Edwards CQ, Adams PC, et al. A survey of 2,851 patients with hemochromatosis: symptoms and response to treatment. Am J Med 1999;106:619-24.
22. Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T. Penetrance of 845G—> A (C282Y) HFE hereditary haemochromatosis mutation in the USA. Lancet 2002;359:211-8.
23. Alizadeh BZ, Njajou OT, Hazes JM, Hofman A, Slagboom PE, Pols HA, et al. The H63D variant in the HFE gene predisposes to arthralgia, chondrocalcinosis and osteoarthritis. Ann Rheum Dis 2007;66:1436-42.
24. Ellervik C, Birgens H, Tybjaerg-Hansen A, Nordestgaard BG. Hemochromatosis genotypes and risk of 31 disease endpoints: meta-analyses including 66,000 cases and 226,000 controls. Hepatology 2007;46:1071-80.
25. Pietrangelo A. Hereditary hemochromatosis — a new look at an old disease. N Engl J Med 2004;350:2383-97.
26. Richette P, Eymard C, Deberg M, Vidaud D, de Kerguenec C, Valla D, et al. Increase in type II collagen turnover after iron depletion in patients with hereditary haemochromatosis. Rheumatology 2010;49:760-6.
27. Olynyk J, Hall P, Ahern M, Kwiatek R, Mackinnon M. Screening for genetic haemochromatosis in a rheumatology clinic. Aust NZ J Med 1994;24:22-5.
28. Bywaters EG, Hamilton EB, Williams R. The spine in idiopathic haemochromatosis. Ann Rheum Dis 1971;30:453-65.
29. Hamilton EB, Bomford AB, Laws JW, Williams R. The natural history of arthritis in idiopathic haemochromatosis: progression of the clinical and radiological features over ten years. Q J Med 1981;50:321-9.
30. de Vernejoul MC, Pointillart A, Golenzer CC, Morieux C, Bielakoff J, Modrowski D, et al. Effects of iron overload on bone remodeling in pigs. Am J Pathol 1984;116:377-84.
31. Diamond T, Stiel D, Posen S. Effects of testosterone and venesection on spinal and peripheral bone mineral in six hypogonadal men with hemochromatosis. J Bone Miner Res 1991;6:39-43.
32. Guggenbuhl P, Filmon R, Mabilleau G, Basle MF, Chappard D. Iron inhibits hydroxyapatite crystal growth in vitro. Metabolism 2008;57:903-10.
33. McDermott JH, Walsh CH. Hypogonadism in hereditary hemochromatosis. J Clin Endocrinol Metab 2005;90:2451-5.