BRIEF OBSERVATION

THE AMERICAN JOURNAL of MEDICINE®

Hereditary Hemochromatosis as a Risk Factor for Joint Replacement Surgery

Enijad Sahinbegovic, MD,[a]* Tomáš Dallos, MD,[a,c]* Elmar Aigner, MD,[b]* Roland Axmann, MD,[a] Matthias Engelbrecht,[a] Maximilian Schöniger-Hekele, MD,[d] Thomas Karonitsch, MD,[e] Martin Farkas, MD,[f] Thomas Karger, MD,[g] Johann Willeit, MD,[h] Ulrich Stölzel, MD,[i] Gernot Keyßer, MD,[j] Christian Datz, MD,[b] Stefan Kiechl, MD,[h] Georg Schett, MD,[a] Jochen Zwerina, MD[a]

[a]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Germany; [b]Department of Internal Medicine, Hospital Oberndorf, Austria; [c]2nd Department of Paediatrics, Medical Faculty, Comenius University Bratislava, Slovakia; [d]Department of Internal Medicine 3, Division of Gastroenterology, Medical University of Vienna, Austria; [e]Department of Internal Medicine 3, Division of Rheumatology, Medical University of Vienna; [f]Department of Internal Medicine, Hospital Wiener Neustadt, Austria; [g]Rheumapraxis Cologne, Germany; [h]Department of Neurology, Medical University of Innsbruck, Austria; [i]Department of Medicine 2, Hospital Chemnitz, Chemnitz, Germany; [j]Department of Internal Medicine I, Martin-Luther-University Halle-Wittenberg, Halle/Saale, Germany.

ABSTRACT

OBJECTIVE: Hemochromatosis is an inherited disease with iron overload and joint involvement resembling osteoarthritis. To determine the rate of joint replacement surgery in patients with hemochromatosis, we performed a cross-sectional cohort study.

METHODS: A total of 199 individuals with hereditary hemochromatosis were included. The prevalence of joint replacement surgery in hip, knee, and ankle joints because of secondary osteoarthritis was assessed. Data were compared with 917 healthy subjects from the population-based Bruneck study.

RESULTS: A total of 32 of 199 individuals with hemochromatosis received joint replacement surgery with a total number of 52 joints replaced. Compared with expected rates in healthy individuals, patients with hemochromatosis had a significantly higher risk for joint replacement surgery (odds ratio 9.0; confidence interval, 4.6-17.4). Joint replacement occurred significantly earlier in life in patients with hemochromatosis; 21.9% of the patients with hemochromatosis and 1.7% of healthy individuals required joint replacement before the age of 50 years ($P = .0027$). Moreover, patients with hemochromatosis were more likely to require multiple joint replacements (8.5%) than the control group (expected rate 0.3%; $P = .0001$).

CONCLUSION: Hemochromatosis is a risk factor for joint replacement surgery because of severe *secondary* osteoarthritis.

 • *The American Journal of Medicine (2010) 123, 659-662*

KEYWORDS: Arthritis; Hemochromatosis; Osteoarthritis; Total joint replacement

Hereditary hemochromatosis is characterized by progressive iron overload confined to certain organs. Liver fibrosis progressing to cirrhosis and hepatocellular carcinoma and cardiomyopathy are potentially fatal conditions.[1] Early detection of hemochromatosis and phlebotomy treatment can prevent excess morbidity and mortality.[2] Most patients with clinically overt hemochromatosis harbor the C282Y homozygous mutation in the HFE gene and have high serum ferritin levels at diagnosis.[3]

Funding: This study is funded by grants from the German Society of Rheumatology (JZ and GS), Articulum Fellowship (TD), ANCYLOSS project of the Bundes-ministerium für Bildung und Forschung (BMBF; to GS), Spondyloarthritis Immunology Research Alliance (SpIRAL), Masterswitch, Kinacept, and Adipoa projects of the European Union (all GS), and Interdisciplinary Centre for Clinical Research at the University of Erlangen (JZ and GS).

Conflict of Interest: None of the authors have any conflicts of interest associated with the work presented in this manuscript.

Authorship: All authors had access to the data and played a role in writing this manuscript.

*These authors contributed equally.

Reprint requests should be addressed to Jochen Zwerina, MD, Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, Krankenhausstrasse 12, 91054 Erlangen.

E-mail address: jochen.zwerina@uk-erlangen.de

0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2010.01.024

In 1964, Schumacher[4] first described a specific arthropathy in patients with hemochromatosis presenting as arthritis of the second and third metacarpophalangeal joints and clinically resembling osteoarthritis. However, the actual disease burden of arthritis in these patients is uncertain, although it is often the initial clinical manifestation of disease.[5] This study assessed the rate of joint replacement surgery as a hard end point for joint failure in patients with hemochromatosis.

CLINICAL SIGNIFICANCE

- Individuals with hemochromatosis have a higher risk for developing severe osteoarthritis of the large joints (knee, hip, ankle) necessitating joint replacement surgery.
- Affected individuals undergo joint replacement surgery earlier in life and have multiple joints replaced compared with a healthy population.

MATERIALS AND METHODS

Design Overview

From 2005 to 2008, subjects with hereditary hemochromatosis were recruited from 7 centers for a cross-sectional prospective study on the clinical phenotype of patients with hemochromatosis and iron overload. Inclusion criteria were as previously described.[6] Briefly, patients had to have serologic signs of iron overload with an increased transferrin saturation (>55% for men, >45% for women). Individuals were included when they had provisional iron overload (serum ferritin > 300 ng/mL for men and postmenopausal women, > 200 ng/mL for premenopausal women) or documented iron overload (serum ferritin > 1000 ng/mL or hepatic iron overload on biopsy). By using patient databases from each center, we identified 350 eligible subjects. A total of 219 subjects volunteered and were screened, with 199 of them fulfilling inclusion criteria and having a complete dataset. All subjects gave written informed consent, and local ethics committees approved this study.

Participants were administered a detailed questionnaire including demographic data. Information on HFE genotype, initial serum ferritin values, transferrin saturation, and the number of phlebotomies was recorded, and ethylenediaminetetraacetic acid blood for confirmatory HFE genotyping was drawn. The number and type of joint replacement surgeries for severe osteoarthritis were recorded. Non-rheumatologic disease manifestations of hemochromatosis, including liver disease, cardiac involvement, diabetes, and hypogonadism, were assessed.

As a reference cohort, the Bruneck Study, a prospective population-based survey on the epidemiology and pathogenesis of cardiovascular and musculoskeletal disease including osteoarthritis, was used.[7] At the 1990 baseline, the study population was recruited as a random sample, stratified according to gender and age, of all inhabitants of Bruneck (125 women and 125 men in each of the fifth to eighth decades of age). Some 93.6% participated, with data assessment completed in 919 subjects. Follow-up examinations were performed every 5 years, and information on joint replacement surgery was complete in 917 individuals (>99%). Details on incident knee and hip replacement surgery in the Bruneck Study and their predictive factors have been described.[7]

Statistical Analysis

Descriptive cohort characteristics are presented as mean ± standard deviation. Frequency of joint replacement because of osteoarthritis in patients with hemochromatosis and individuals from the population-based Bruneck Study with normal ferritin levels was compared by multivariate analysis adjusted for age, gender, menopausal status, presence of diabetes, C-reactive protein level, and body mass index. All reported P values are 2 sided. Statistical analysis was performed using PASW 17.0.2 and SPSS 15.0 statistical software (SPSS Inc, Chicago, Ill).

RESULTS

This cohort included 199 subjects with hemochromatosis, of whom 134 were male (67.3%) and 65 were female (32.7%; Table). Their mean age at inclusion was 55.9 years (standard deviation ± 12.2 years, range 25-79). Hemochromatosis had been diagnosed at a mean age of 49.6 years (± 11.9 years) with a mean duration of symptoms of 3.8 years (± 12.0 years). Serum ferritin values at diagnosis were 2090 ± 2173 ng/mL. The majority of subjects were C282Y homozygous (88.4%). According to inclusion criteria,[6] 113 participants (56.8%) had documented iron overload, and 86 participants (43.2%) had provisional iron overload.

Thirty-two subjects (16.1%, 18 male, 14 female, ratio 1.3:1) underwent total joint replacement for severe osteoarthritis. The mean age at joint replacement surgery was 58.3 ± 10.4 years. A total number of 52 joints were replaced. Fifteen subjects (46.6%) had 1 joint replaced, 14 subjects (43.8%) had 2 joints replaced, and 3 subjects (9.4%) had 3 joints replaced. The most common localization was the hip (44 joints, 84.6%), whereas knee (6 joints) and ankle joint replacements (2 joints) were less frequent.

To assess the specific contribution of hemochromatosis to joint replacement, we performed a multivariate comparison with healthy individuals (n = 824) with normal ferritin levels (Bruneck cohort). After adjustment for potential confounders, a significantly increased risk for joint replacement surgery among patients with hemochromatosis (odds ratio 9.0; confidence interval, 4.6-17.4; $P = 8.71 \times 10^{-11}$) was found. When calculating age- and gender-specific intervention rates on the basis of the data from the Bruneck cohort, the expected prevalence for joint replacement because of severe

Table Clinical Characteristics

Demographic Variables	
No. of patients (N)	199
Gender male/female (No., %)	134 (67.3%)/65 (32.7%)
Age at inclusion (mean ± SD, range; y)	55.9 ± 12.2, 25-79
Body mass index (mean ± SD)	26.6 ± 3.9
Smoking (No., %)	105 (52.8%)
Alcohol intake (No., %)	128 (64.3%)
Disease-specific variables	
Age at HFE diagnosis (mean ± SD y)	49.6 ± 11.9
Onset of symptoms (mean ± SD y)	3.8 ± 12.0
Highest ferritin (mean ± SD, median/range; ng/mL)	2090 ± 2173; 1218, 261-14,080
Phlebotomy therapy (No., %)	182 (91.5%)
Start of phlebotomy therapy (mean ± SD; y)	49.7 ± 11.6
Duration of phlebotomy therapy (mean ± SD; y)	5.9 ± 6.8
Total No. of phlebotomies (mean ± SD)	51.4 ± 62.0
Genotype	
C282Y homozygous (No., %)	176 (88.4%)
Compound heterozygous (No., %)	13 (6.5%)
Others (No., %)[a]	10 (5.0%)
Organ involvement	
Aminotransferase elevation	81 (41.5%)
Liver fibrosis/cirrhosis	36 (18.1%)
Diabetes	27 (13.6%)
Cardiomyopathy	22 (11.1%)
Patients with joint replacement	
No. of patients (%)	32 (16.1%)
Male/female (No., %)	18 (56.3%)/14 (43.7%)
Age at first joint replacement (mean ± SD y)	58.3 ± 10.4
Total No. of joint replacements	52
No. of joint replacements per patient	
1 (No., %)	15 (46.9%)
2 (No., %)	14 (43.8%)
3 (No., %)	3 (9.4%)
Localization of joint replacement	
Hip (No., %)	44 (84.6%)
Knee (No., %)	6 (11.5%)
Ankle (No., %)	2 (3.8%)

SD = standard deviation.
[a]C282Y heterozygous 4 (2.0%), H63D homozygous 2 (1.0%), H63D heterozygous 1 (0.5%), juvenile HFE 1 (0.5%), t+IVS2+4T/C+IVS2+4T/C 1 (0.5%), R226W/C282Y 1 (0.5%).

osteoarthritis was only 2.0% as opposed to 16.1% actually affected in the hemochromatosis group ($P < .000001$). Moreover, patients with hemochromatosis were more likely to require multiple joint replacement surgeries (8.5%) than the control group (expected rate 0.3%; $P = .0001$). Finally, subjects with hemochromatosis underwent joint replacement surgery earlier in life (Figure); 21.9% (50.0%) of the subjects with hemochromatosis and 1.7% (8.6%) of healthy individuals required joint replacement before age 50 years (age 60 years) ($P = .0027$ and $P = 8.9 \times 10^{-6}$, respectively).

DISCUSSION

Hemochromatosis is associated with a high risk of joint replacement surgery, highlighting the strong association between iron overload and degenerative joint disease. Our data demonstrate that *secondary* osteoarthritis is not only a central component of hemochromatosis but also a major disease burden. We found that 16% of subjects with hemochromatosis had at least 1 joint replaced, which indicates that a substantial proportion of subjects with hemochromatosis face progressive and severe osteoarthritis warranting joint replacement surgery. This notion is further supported by a highly increased risk for multiple joint replacements and a substantially lower age at intervention. When comparing the risk for joint replacement surgery in patients with hemochromatosis and the general population, a 9-fold risk in patients with hemochromatosis could be documented after adjustment for potential confounders. Because the rate of joint replacements in the Bruneck Study population corresponds well to overall joint replacement rates in the general population, hemochromatosis emerges as a strong enhancer of the risk of osteoarthritis.

It is likely that some patients requiring joint replacement have unrecognized hemochromatosis. This concept is not only favored by the strong association of hemochromatosis

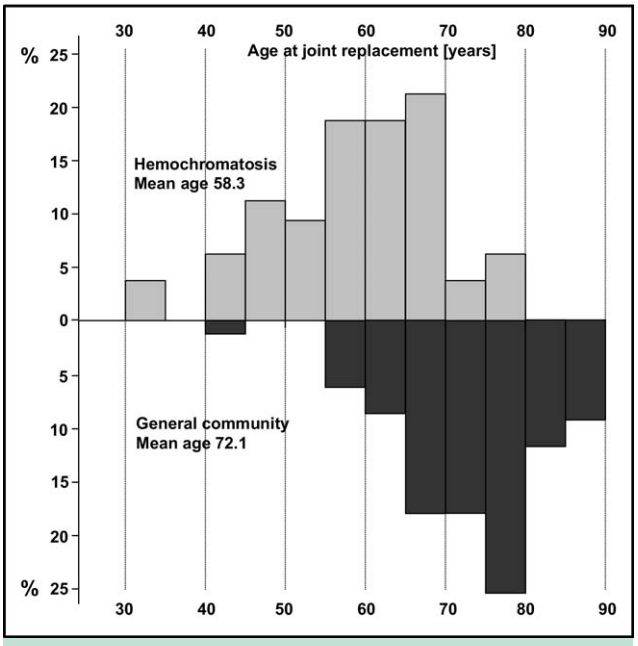

Figure Age-related distribution of joint replacement surgery in the hemochromatosis cohort (upper panel, *light grey bars*) and the general community (lower panel, *dark grey bars*).

with the prevalence of joint replacement surgery but also supported by several other observations: arthritis is a common clinical manifestation in patients with hemochromatosis,[8] but knowledge on the distribution and severity of arthritis in this patient group is so far scarce.[9] Arthritis, in contrast with other clinical features of hemochromatosis, is not considered to be reversible in the majority of patients,[10] and thus likely progresses to joint failure. Only a fraction of patients with hemochromatosis have clinically overt organ involvement despite iron overload. Such patients might easily escape diagnosis for hemochromatosis but clinically show premature osteoarthritis as the sole clinical manifestation of iron overload. It is noteworthy that iron overload is a key pathognomonic feature of the disease, because individuals with HFE gene mutations but no iron overload do not develop disease.[11] We therefore included subjects with HFE gene mutation and documented or provisional iron overload in this cohort regardless of clinical manifestations attributed to hemochromatosis.

STUDY LIMITATIONS

We attempted to eliminate bias leading to preferential inclusion of patients with HFE with arthropathy by recruiting a significant proportion of subjects in non-rheumatology centers (64.8% of all subjects). The prevalence of other clinical manifestations related to hemochromatosis was similar to previously published cohort and population-based studies. Also, asymptomatic patients identified by an accidental finding of pathologic iron metabolism parameters and by screening of relatives of affected patients were not excluded from our study.[6] More important, the prevalence of our primary end point (joint replacement) was not significantly different between patients originating from rheumatology and non-rheumatology centers (15.7% vs 16.3%).

CONCLUSIONS

These data show that hemochromatosis leads to *secondary* osteoarthritis of multiple joints early in life, which results in joint failure and a high rate of replacement surgery.

References

1. Adams PC, Barton JC. Haemochromatosis. *Lancet.* 2007;370:1855-1860.
2. Niederau C, Fischer R, Purschel A, et al. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology.* 1996; 110:1107-1119.
3. Datz C, Lalloz MR, Vogel W, et al. Predominance of the HLA-H Cys282Tyr mutation in Austrian patients with genetic haemochromatosis. *J Hepatol.* 1997;27:773-779.
4. Schumacher HR Jr. Hemochromatosis and arthritis. *Arthritis Rheum.* 1964;7:41-50.
5. Schmid H, Struppler C, Braun GS, et al. Ankle and hindfoot arthropathy in hereditary hemochromatosis. *J Rheumatol.* 2003;30:196-199.
6. Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. *N Engl J Med.* 2008; 358:221-230.
7. Schett G, Kiechl S, Bonora, E, et al. Vascular cell adhesion molecule-1 as a predictor for severe osteoarthritis of hip and knee joints. *Arthritis Rheum.* 2009;60:2381-2389.
8. Valenti L, Fracanzani AL, Rossi V, et al. The hand arthropathy of hereditary hemochromatosis is strongly associated with iron overload. *J Rheumatol.* 2008;35:153-158.
9. Sinigaglia L, Fargion S, Fracanzani AL, et al. Bone and joint involvement in genetic hemochromatosis: role of cirrhosis and iron overload. *J Rheumatol.* 1997;24:1809-1813.
10. McDonnell SM, Preston BL, Jewell SA, et al. A survey of 2,851 patients with hemochromatosis: symptoms and response to treatment. *Am J Med.* 1999;106:619-624.
11. Waalen J, Nordestgaard BG, Beutler E. The penetrance of hereditary hemochromatosis. *Best Pract Res Clin Haematol.* 2005;18:203-220.