Rheumatology Advance Access published January 12, 2013

Original article

doi:10.1093/rheumatology/kes392

Idiopathic hand osteoarthritis *vs* haemochromatosis arthropathy—a clinical, functional and radiographic study

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Abstract

Objective. Haemochromatosis arthropathy is a secondary OA and the most frequent and earliest clinical presentation of hereditary haemochromatosis (HH). The aim of this study was to perform a direct clinical, functional and radiographic comparison with idiopathic hand OA (HOA) to unravel important differences between these clinical entities.

Methods. In total, 299 patients (141 with HH arthropathy of the hands and 158 patients with idiopathic HOA) were recruited. Structured clinical assessment including hand function tests, as well as hand radiographs with scoring according to Kellgren–Lawrence, were carried out in all patients.

Results. HH arthropathy and HOA differed significantly: patients with HH arthropathy were younger and predominantly male as compared with HOA. In males but not females, HH arthropathy led to an earlier start of symptoms than in HOA. Patients with HOA had more tender joints and worse hand function than patients with HH arthropathy, although subjective measures of joint pain and function were similar. MCP and wrist joint involvement was more frequent and severe in HH arthropathy, while HOA patients more frequently had degenerative changes in the first CMC as well as PIP and DIP joints.

Conclusion. HH arthropathy and idiopathic HOA differ significantly in terms of epidemiology, localization, severity of symptoms and radiographic changes.

Key words: osteoarthritis, haemochromatosis, radiological characteristics.

Introduction

OA of the hand is a highly prevalent condition [1]. Increased age, female gender and obesity have been identified as risk factors for hand OA (HOA) in accordance with findings in knee OA [2, 3]. DIP joints as well as the first CMC joint appear to be the most prevalent joint localizations affected by HOA. HOA can cause significant pain to patients and impair quality of life [4].

Hereditary haemochromatosis (HH) is an inherited disease causing progressive iron overload confined to solid organs such as the liver, heart and pancreas. Most patients with clinically overt HH harbour the C282Y homozygous mutation [5–7]. Serum ferritin levels are elevated at diagnosis. Liver fibrosis progressing to cirrhosis and finally development of hepatocellular carcinoma as well as cardiomyopathy are potentially fatal conditions.

Haemochromatosis arthropathy is a common form of secondary OA first described by Schumacher in 1964 [8]. Joint pain is the key clinical manifestation. Progressive and severe joint damage occurs, resulting in a significant risk for joint replacement surgery in large joints [9]. Importantly, arthropathy is the most prevalent and often the earliest clinical manifestation of HH and its

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Submitted 8 August 2012; revised version accepted 21 November 2012.

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CLINICAL SCIENCE

early recognition is a unique opportunity to prevent progressive organ damage due to continued iron overload and hence is clinically relevant.

The clinical picture is thought to be characteristic; hand joints are frequently involved, with the second and third MCP joints being typically affected. However, patients also suffer from symptoms in other hand joints [10]. Chondrocalcinosis in the wrist and knee joints and hook-like osteophytes are characteristic; nonetheless, the radiographic changes may be difficult to distinguish from HOA. In fact, the exact similarities and differences between HH arthropathy and HOA in terms of clinical presentation, severity of disease and radiographic changes are currently incompletely understood. Due to a potentially high degree of overlap of the usually unspecific clinical findings, differentiation from HOA may be problematic in clinical practice.

So far, no direct comparison between cohorts of patients with HOA and HH arthropathy has been undertaken. In an attempt to better characterize HH arthropathy, we assessed the prevalence and distribution of clinical and radiographic signs in patients with genetically confirmed HH showing iron overload and symptomatic joint disease and compared these findings with a cohort of patients with idiopathic HOA.

Methods

Patients

Both idiopathic HOA and HH arthropathy patients originated from cohorts that have been characterized before.

HOA cohort

Consecutive patients with HOA according to the ACR criteria for HOA presenting at the outpatient clinic of the Medical University of Vienna were collected [11]. A total of 158 patients who had X-rays of the hand and a complete clinical data set available were included. Patients with isolated CMC joint involvement were not included. Patients with evidence of any rheumatic disease other than OA or iron overload (elevation of ferritin levels above the upper limit of normal) were excluded.

HH cohort

HH patients were recruited for a cross-sectional multicentre prospective study on the clinical phenotype of patients with haemochromatosis and iron overload between 2005 and 2008 in seven rheumatology and gastroenterology centres in Austria and Germany. Details of inclusion criteria have been previously described [12]. In this analysis, 141 of the original 199 patients were included who presented with symptoms in the hand joints and, at the same time, had radiographs of hands available. To avoid the inclusion of patients with arthralgia without clear evidence of arthropathy, only HH patients with at least one radiographic change in any hand joint were included.

All participants were informed in detail about the study procedures and gave written informed consent according to the Declaration of Helsinki. The local institutional ethics committees (University of Erlangen-Nuremberg, Germany; Medical University of Vienna and Hospital Oberndorf, Austria) approved the study.

Clinical assessment

All patients from both cohorts underwent clinical evaluation by a single experienced rheumatologist (E.S.) at inclusion into both studies. Examinations comprised the assessment of the number of tender, swollen and bony swollen joints using a 66-joint count. Additionally, hand function was determined by two standardized tests: (i) grip strength measured by a vigorimeter and (ii) Moberg's picking-up test [13]. Patients' assessment of their hand function and pain as well as disease activity and fatigue were determined using a visual analogue scale (VAS).

Radiographic assessment

Standard hand radiographs (anteroposterior and oblique) of all patients were evaluated. A single experienced blinded reader (E.S.) performed the evaluation of all hand radiographs. A modified Kellgren–Lawrence score (including also CMC joints) was used for the assessment of 32 joints of both hands (2 radiocarpal, 2 CMC, 8 DIP, 10 PIP and 10 MCP). The degree of radiographic changes was assessed semi-quantitatively by a modified Kellgren–Lawrence score as follows: 0–3 points for joint space narrowing; 0–2 points for osteophytes; 0–3 points for sclerosis; 0–2 points for deformity. Grading of individual joints was determined as follows: 0 points = grade 0; 1–2 points = grade 1; 3–4 points = grade 2; 5–9 points = grade 3; 10 points = grade 4. Grading obtained for HOA and HH arthropathy was compared statistically. Additionally, the presence or absence of erosions/cysts and chondrocalcinosis was documented, as these are important radiographic features of haemochromatosis arthropathy [10]. To visualize the different prevalence of individual features in OA and HH, acquired data were plotted in a three-dimensional graph (Fig. 1).

Statistical analysis

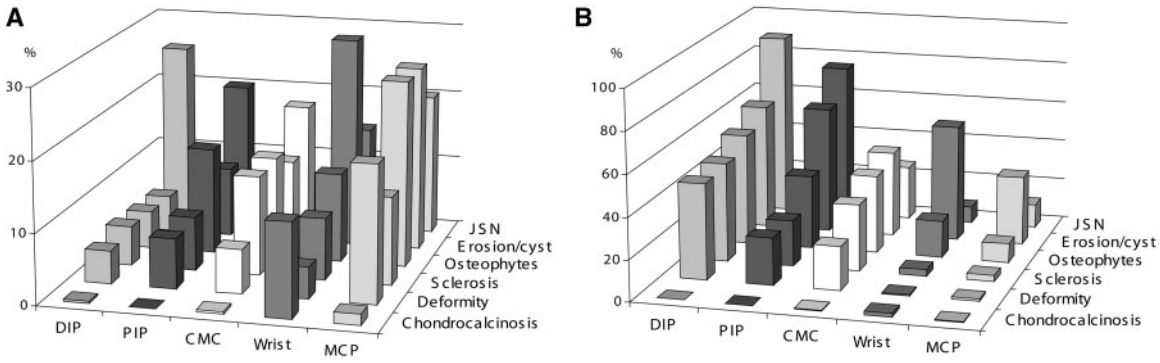
For descriptive statistics, means of age, BMI and clinical assessment scores were calculated and expressed as mean (S.D.). Prevalences were estimated as observed proportions and expressed as a percentage of the total number of subjects. Significance of differences was calculated using *t*-test for data with normal distribution and χ^2-test for comparison of prevalences between compared groups. A $P \leqslant 0.05$ was considered significant.

Results

Clinical characteristics of haemochromatosis and HOA patients

A total of 158 idiopathic HOA patients and 141 HH arthropathy patients were included in this study. Clinical data are given in Table 1. A more detailed characterization of the HH cohort has been provided previously [12]. As expected, HH arthropathy patients were predominantly

FIG. 1 Prevalence of radiographic features in hand joints of patients with (**A**) HH arthropathy and (**B**) primary HOA.



JSN: joint space narrowing.

TABLE 1 Characteristics of study cohorts

Cohort	Haemochromatosis	HOA	*P*
Patients, *n*	141	158	–
Male/female, *n* (%)	96 (68.1)/45 (31.9)	14 (8.9)/144 (91.1)	0.001
Age, mean (S.D.), years	58.7 (11.1)	62.4 (7.9)	0.001
BMI mean (S.D.)	26.1 (3.5)	26.4 (4.3)	0.58
Smoking, *n* (%)	89 (63.12)	69 (43.7)	0.16
Alcohol, *n* (%)	109 (77.3)	80 (50.6)	0.06
Age at diagnosis of haemochromatosis, mean (S.D.), years	51.6 (11.5)	NA	NA
Highest serum ferritin level, median (range), ng/ml	1218 (275–14 080)	NA	NA
Phlebotomy therapy, *n* (%)	133 (94.3)	NA	NA
Age at start of phlebotomy therapy, mean (S.D.), years	52.0 (11.0)	NA	NA
Duration of phlebotomies, mean (S.D.), years	6.6 (7.9)	NA	NA
Total number of phlebotomies, mean (S.D.)	56.2 (67.1)	NA	NA
Haemochromatosis genotype, *n* (%)			
C282Y homozygous	127 (90.1)	NA	NA
Compound heterozygous	7 (5.0)	NA	NA
Others[a]	10 (5.0)	NA	NA

[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%). NA: not applicable.

male, whereas the majority of HOA patients were female. HH arthropathy patients were slightly younger than HOA patients. Overall, smoking habits and BMI were not different between groups, while alcohol consumption was more frequent among HH arthropathy patients. Due to the gender imbalance between cohorts, we decided to perform further analyses for each gender separately.

Self-reported musculoskeletal symptoms

Joint complaints occurred at an earlier age and thus the duration of joint complaints in male HH arthropathy patients was significantly longer than in male HOA patients. There was no difference in the onset of joint complaints in female patients. However, subjective measures of hand function and pain based on VASs were not different among male haemochromatosis and HOA patients. Female HOA patients reported slightly worse hand pain and function as determined by VASs (Table 2).

Clinical assessment of hand involvement

Tender joints were significantly more prevalent in female HOA subjects as compared with HH arthropathy patients. Although bony swelling of joints was generally more prevalent in HOA patients, the difference in bony swollen joint counts did not reach statistical significance. Bony swelling was the most common objective finding in both cohorts, present in 104 (73.8%) subjects with HH arthropathy and all subjects with HOA. Swelling had a very low prevalence and was not significantly different between cohorts for both sexes.

Objective measures of hand function

Grip strength was significantly higher for the dominant and non-dominant hand in HH arthropathy as compared with HOA patients. Similarly, haemochromatosis patients performed better in Moberg's picking-up test

Table 2 Rheumatic signs and symptoms in haemochromatosis arthropathy and idiopathic HOA

Gender	Male			Female		
Cohort	Haemochromatosis	HOA	*P*	Haemochromatosis	HOA	*P*
Self-reported rheumatic symptoms						
Age at initial joint complaints, mean (S.D.), years	48.0 (12.0)	58.4 (12.0)	0.008	47.8 (12.8)	52.1 (11.2)	0.05
Duration of joint complaints, mean (S.D.), years	12.0 (10.5)	7.3 (5.2)	0.02	12.8 (13.3)	10.0 (9.6)	0.17
VAS hand function (0–100), mean (S.D.), mm	39.7 (28.5)	39.1 (18.7)	0.94	35.8 (26.6)	46.7 (20.4)	0.005
VAS hand pain (0–100), mean (S.D.), mm	28.0 (25.0)	28.1 (20.1)	0.99	24.9 (26.7)	35.7 (21.4)	0.006
VAS disease activity (0–100), mean (S.D.), mm	32.5 (24.5)	34.4 (25.4)	0.79	34.4 (24.2)	37.2 (22.5)	0.47
VAS fatigue (0–100), mean (S.D.), mm	34.0 (29.0)	27.8 (29.8)	0.46	42.8 (27.9)	35.3 (27.5)	0.12
Objective measures of hand function						
Grip strength—dominant hand, mean (S.D.), bar	0.69 (0.34)	0.32 (0.25)	<0.001	0.59 (0.18)	0.23 (0.19)	<0.001
Grip strength—non-dominant hand, mean (S.D.), bar	0.73 (0.35)	0.25 (0.24)	<0.001	0.56 (0.19)	0.21 (0.19)	<0.001
MPUT—dominant hand, mean (S.D.), s	13.5 (3.8)	23.7 (25.5)	0.001	11.8 (3.2)	15.5 (6.1)	<0.001
MPUT test—non-dominant hand, mean (S.D.), s	13.2 (3.5)	20.8 (16.1)	<0.001	11.8 (2.5)	14.9 (5.5)	<0.001
Physician's assessment						
Tender joint count ⩾ 1, *n* (%)	43 (44.8)	9 (64.3)	0.25	28 (62.2)	123 (85.4)	0.001
Tender joint count (0–32), mean (S.D.)	2.1 (4.1)	2.1 (2.1)	0.95	2.3 (3.0)	7.3 (7.6)	<0.001
Bony swollen joint count ⩾ 1, *n* (%)	72 (75.0)	14 (100.0)	0.04	32 (72.1)	144 (100.0)	<0.001
Bony swollen joint count (0–32), mean (S.D.)	9.7 (9.3)	7.6 (4.4)	0.42	6.8 (8.0)	8.2 (5.3)	0.15
Swollen joint count ⩾ 1, *n* (%)	16 (16.7)	1 (7.1)	0.69	7 (15.6)	27 (18.8)	0.82
Swollen joint count (0–32), mean (S.D.)	0.5 (1.62)	0.1 (0.3)	0.32	0.4 (1.1)	0.4 (1.1)	0.90

Higher VAS values are associated with worse hand function, more pain, higher disease activity and more fatigue. MPUT: Moberg's picking-up test.

for both dominant and non-dominant hands. Thus, although differences in subjective measures of hand function were not significantly different between HH arthropathy and HOA patients, objective measures revealed a significantly better hand function in HH arthropathy patients.

Distribution of radiographic features

To determine the pattern of joint involvement, the presence of any radiographic change was recorded in both cohorts and expressed as the percentage of joints affected by each respective radiographic feature as well as the severity of the affection according to the modified Kellgren–Lawrence score. No significant differences in the distribution of radiographic changes were noted among genders. Thus radiographic data could be analysed without distinction between the genders.

In HH arthropathy patients, a clearly different pattern of joint involvement than in HOA could be observed (Fig. 1). Significant differences in the prevalence of nearly all radiographic features were noted. Except for erosions/cysts, the prevalence of all radiographic features, and thus also the severity of joint involvement as assessed by the modified Kellgren–Lawrence score, was significantly higher in the MCP joints of HH arthropathy patients as compared with HOA. Conversely, DIP, PIP and first CMC joints were more severely affected in HOA (Table 3). As expected, chondrocalcinosis was significantly more prevalent in HH patients than in HOA patients (17.0 *vs* 2.5%, respectively, $P < 0.001$). All OA patients with chondrocalcinosis had normal ferritin levels and thus were not considered to have HH.

Table 3 Severity of joint involvement of the joints of the hand as assessed by the modified Kellgren–Lawrence score (maximum 10 points for each joint)

Joints	No. of joints, mean Kellgren–Lawrence score (S.D.)		*P*
	Haemochromatosis	HOA	
DIP	1128, 0.5 (1.0)	1264, 3.9 (3.1)	<0.001
PIP	1410, 0.7 (1.7)	1580, 2.5 (2.6)	<0.001
MCP	1410, 1.1 (2.0)	1580, 0.3 (0.8)	<0.001
Radiocarpal	282, 0.6 (1.6)	316, 0.4 (0.8)	0.006
CMC	282, 0.7 (1.8)	316, 1.7 (2.6)	<0.001

Discussion

To our knowledge, this is the first study to directly compare clinical, functional and radiographic features between haemochromatosis arthropathy and idiopathic HOA. HH arthropathy is the most common form of secondary HOA and frequently the first clinical symptom in HH [14, 15], leading to progressive and severe joint damage that results in a significant risk for joint replacement surgery [16]. Hand joint involvement, particularly of the second and third MCP joints, has been considered a typical feature of HH arthropathy since its first description as a separate clinical entity [17]. However, due to the high degree of overlap of the usually unspecific clinical findings, differentiation from HOA may be problematic in clinical practice. Also, mildly elevated liver enzymes and joint

pain are frequently accepted in clinical practice as part of ageing and lifestyle in middle-aged and elderly patients, thus preventing diagnosis of haemochromatosis.

In our comparative cohort study, male HH arthropathy patients were significantly younger and had longer duration of joint pain at study inclusion. Early onset is characteristic of haemochromatosis arthropathy and is one of the key features that may prompt clinicians to consider HH as the cause of OA. The significant difference in the gender composition of the cohorts is explained by the pathophysiology of iron metabolism, with iron overload occurring at a later age in females due to regular blood loss by menstrual bleeding. To account for gender imbalance, clinical and functional features were assessed separately in males and females in this study. On the other hand, this approach resulted in a rather small number of male idiopathic HOA patients. This may have affected the results of our analysis of male patients, in that some significant results may have been missed.

Hand function, hand pain and disease activity as perceived by patients tended to be, despite the longer duration of joint symptoms, less severe in HH arthropathy as compared with HOA, especially in females. Thus female patients with haemochromatosis had significantly lower tender joint counts than HOA patients. Interestingly, there was no overall difference between HH arthropathy and HOA in physician-assessed bony swollen and swollen joint counts in both males and females. Despite this fact, haemochromatosis patients performed significantly better in objective tests of hand function, which was found in both females and males. We suggest that this finding may relate to the specific distribution of joint involvement in haemochromatosis arthropathy. Functionally relevant joints for hand function such as the first CMC joint were less affected in HH arthropathy, while the impact of MCP joint OA usually spared in HOA on hand function is unclear [18]. Thus, overall, haemochromatosis arthropathy, despite its earlier onset, causes a milder form of HOA with overall better preservation of hand function, which is most likely based on the involvement of a joint pattern different from that of HOA. Our findings, however, may possibly have been affected by, for instance, better neuromuscular function in the younger haemochromatosis patients or by a more severe degree of joint involvement in HOA patients.

Joint space narrowing, erosion and cyst formation, osteophytes and subchondral sclerosis are well-known features of OA; however, they are also characteristic of HH arthropathy. As compared with HH arthropathy patients, most radiographic features were significantly more prevalent in HOA joints, reflecting a more severe disease. This is particularly the case for the involvement of the PIP joints, DIP joints and the first CMC joint. Especially the latter is important for hand function, and our radiographic findings support the clinical findings of preserved hand function in HH arthropathy. However, some joints are more affected in HH arthropathy than in HOA patients. Degenerative MCP joint changes and chondrocalcinosis of the wrist were far more frequently observed in HH arthropathy than in HOA.

Our study has some limitations. First, different recruitment strategies were used for the compared cohorts. Although HH is a relatively common genetically determined disease, due to its low penetrance, recruitment of sufficient numbers required several centres. On the other hand, idiopathic HOA patients were recruited in a single academic rheumatology centre in a single country. Secondly, different inclusion criteria were used for the OA and HH cohort. For HOA, clinical ACR criteria were used. For HH patients to be included, combined clinical and radiographic criteria were used. This definition of HH arthropathy was required in order to avoid the inclusion of HH patients with arthralgia without definite radiographic signs of degenerative joint disease, which is quite common in HH patients. We can therefore not exclude a possible bias resulting from these different recruitment and inclusion strategies. Thirdly, the different age and gender composition of the cohorts, resulting from the natural course of the diseases, limits the assessment of hand function and our results warrant further confirmation.

In summary, HOA resulting from iron overload in HH is significantly different from HOA, with MCP joints being most severely affected. In spite of an earlier onset of clinical symptoms, HH patients have better hand function than HOA patients. Further research is required to define sensitive and specific diagnostic criteria for haemochromatosis arthropathy.

Rheumatology key message

- Haemochromatosis hand arthropathy predominantly affects MCP joints and frequently causes chondrocalcinosis.
- Hand function is less affected in haemochromatosis arthropathy than in idiopathic HOA.

Acknowledgements

We thank Gernot Keyßer (Department of Internal Medicine I, Martin-Luther-University Halle-Wittenberg, Halle/Saale, Germany), Ulrich Stölzel (Department of Medicine 2, Hospital Chemnitz, Chemnitz, Germany), Thomas Karger (Rheumapraxis Cologne, Germany), Martin Farkas (Department of Internal Medicine 1, Hospital Wiener Neustadt, Austria), Thomas Karonitsch, Josef Smolen and Maximilian Schöniger-Hekele (all Department of Internal Medicine 3, Medical University of Vienna, Austria) for recruiting haemochromatosis patients for this study. We are grateful to Franz Kainberger (Department of Radiology, Medical University of Vienna, Austria) for providing support to score radiographs from the ViHOA cohort. T.D. was supported by a Pfizer Articulum Fellowship.

Funding: This study was supported by the German Society of Rheumatology (start-up grant to J.Z.) and the Austrian Science Fund (FWF): KLI123.

Disclosure statement: The authors have declared no conflicts of interest.

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