

Haemochromatosis: unexplained metacarpophalangeal or ankle arthropathy should prompt diagnostic tests: findings from two UK observational cohort studies

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Objectives: To examine demographic and clinical features leading to the diagnosis of hereditary haemochromatosis and assess factors that might enhance earlier diagnosis, with particular attention to arthritic symptoms.

Method: Diagnostic features were captured directly from patients with haemochromatosis attending a specialist rheumatology clinic (group 1) and from analysis of a specifically designed questionnaire circulated to members of the UK Haemochromatosis Society (group 2).

Results: In groups 1 (n = 62) and 2 (n = 470), respectively, the diagnosis of haemochromatosis was made at a mean age of 52.8 and 56.4 years with 77% and 76% reporting joint symptoms with a mean duration of 8.3 and 8.1 years. The first joints to be affected in group 1 were the metacarpophalangeal (MCP; 38.5%) and ankle (29.5%) followed by the knee, hip, and proximal interphalangeal (PIP) joints. At the time of clinical assessment or questionnaire completion, the most prevalent regions with arthropathy in group 1 were PIP (64.5%), knee (64%), ankle (61%), and MCP (60%) and in group 2 the most prevalent joint regions self-reported were the first carpometacarpal (CMC; 59%), wrist (52%), PIP (47%), MCP (46%), knee (42%), and ankle (35%).

Conclusions: Data from both cohorts confirm the high prevalence of joint symptoms in haemochromatosis predating the diagnosis by many years. Discriminatory features of the arthropathy include the involvement of MCP joints and ankles at a relatively young age in the absence of trauma, all of which are unusual features of primary osteoarthritis (OA). The finding of this presentation should prompt diagnostic tests for haemochromatosis.

Haemochromatosis is an autosomal recessive disorder with low penetrance, in which intestinal iron hyperabsorption leads to tissue iron deposition and organ dysfunction (1). Iron depletion is an effective therapy if commenced early, avoiding many manifestations, such as hepatic and cardiac disease, and reversing others such as fatigue. A pre-venesection serum ferritin < 1000 µg/L is taken to be a marker of good prognosis (2), but in reality delays in securing the diagnosis are the norm and peak ferritin levels are often much higher. The early detection of iron overload and prompt commencement of 'de-ironing' is therefore key to good outcomes for patients with haemochromatosis (3). Where there is a family history of the condition, regular measurement of transferrin saturation and ferritin will secure an early diagnosis. For other patients, detection of iron overload may be serendipitous, for example as a consequence of random testing or part of a non-specific well-person health screen. However, for many patients recognition

of symptoms and signs is required to prompt measurement of iron indices and then gene analysis. Unfortunately, most of the symptoms and signs of iron overload are insufficiently characteristic to prompt early suspicion, and many years often pass before the diagnosis is considered and investigations initiated.

Arthropathy is highly prevalent in patients with hereditary haemochromatosis (2, 4), is significantly associated with a high ferritin level at presentation (2, 5), and has the clinical and radiographic characteristics of osteoarthritis (OA) (6, 7). Although OA is a common condition in the general population, early onset in the absence of trauma or a family history and involvement of unusual sites such as the metacarpophalangeal (MCP) joints may be sufficient clues to act as a diagnostic trigger for haemochromatosis (7). We have examined demographic and clinical features leading to the diagnosis of hereditary haemochromatosis in two large UK patient groups to assess factors that might enhance earlier diagnosis, with particular attention to arthritic symptoms.

Method

Patients attending a specific haemochromatosis arthropathy clinic at St George's University Hospitals National

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Accepted 15 February 2016

Table 1. Demographic, genotype, and diagnostic details.

| | Group 1 (n = 62) | Group 2 (n = 470) |
|---|---------------------|----------------------|
| Female (%) | 56 | 47 |
| <i>C282Y</i> homozygous (%) | 65 | 52 |
| <i>C282Y/WT</i> heterozygous (%) | 2 | 5 |
| <i>C282Y/H63D</i> compound (%) | 6 | 7 |
| <i>H63D</i> homozygous (%) | 2 | 0 |
| <i>H63D</i> heterozygous (%) | 0 | 0.5 |
| Genotype unknown (%) | 26 | 33 |
| Age at diagnosis (years), mean (range) | 52.8 (28–75) | 56.4 (15–83) |
| Time since diagnosis at data collection (years), mean (range) | 6.0 (0.5–21) | 9.4 (0–41) |
| Diagnosis after family screening, n (%) | 9 (15) | 92 (20) |
| Diagnosis after random screening, n (%) | 18 (29) | 112 (25) |
| Diagnosis prompted by symptoms, n (%) | 35 (56) | 250 (55) |
| Serum ferritin at diagnosis (µg/L) | | |
| Mean (range) | 2006 (163–8400) | 1670 (40–15 000) |
| Median | 1100 | (n = 415) 1000 |
| Duration of first attributable symptom at diagnosis (years) | | |
| Median (range) | 5 (0–45) | 4 (0–65) |
| Mean | 6.8 | 8.1 |
| Joint symptoms (%) | 98 | 85 |
| Joint symptoms pre-diagnosis (%) | 77 | 76 |
| > 5 years, n (%) | 25 (40) | 200 (42.5) |
| 1–5 years, n (%) | 21 (34) | 128 (27) |
| 0–1 year, n (%) | 2 (3) | 28 (6) |

Health Service (NHS) Foundation Trust, London were questioned about events leading to diagnosis and examined for signs of arthropathy. Data were entered onto a standard proforma and transferred onto an Excel spreadsheet for analysis using descriptive statistics. A questionnaire was designed to capture diagnostic and arthritis-specific information in patients with haemochromatosis. The questionnaire was pretested with members of the UK Haemochromatosis Society and refined following analysis and discussion. The final version was circulated to all members of the UK Haemochromatosis Society in electronic and paper versions. Responses were either completed electronically and returned by e-mail or completed manually on paper and posted to the UK Haemochromatosis Society, where data were transferred into the electronic version. All responses were entered onto an Excel spreadsheet and analysed using descriptive statistics.

Results

We analysed data from the first 62 consecutive patients (referred to here as group 1) seen in the St George's Haemochromatosis Arthropathy clinic between November 2012 and March 2015. The questionnaire was circulated to approximately 1300 members of the UK Haemochromatosis Society in December 2013 with electronic prompts to return completed forms in February 2014. By April 2014, responses were received from 470 patients (referred to here as group 2). Responses were mostly received from across the UK, and 26 came from

the Republic of Ireland, other EU countries, the USA, Canada, South Africa, Australia, and New Zealand.

Demographic information, genotype, and details relating to the method of diagnosis, ferritin at diagnosis, and duration of pre-diagnostic symptoms for groups 1 and 2 are shown in Table 1.

Group 1: Haemochromatosis Arthropathy clinic

The diagnosis of haemochromatosis had been made on the basis of symptoms in 56% patients (n = 35), with the most frequent symptoms triggering investigations being joint pain in 28 (80%) and fatigue in 22 (63%). When joint pain had prompted investigations (n = 28), the median interval from onset of pain to diagnosis was 6.5 (mean 7.7) years, range 1–22 years. The diagnosis followed random screening in 29% and 17/18 of these patients recalled symptoms at the time, including joint pains in 13 (72%) and fatigue in three (16%). The diagnosis followed family screening in 15% (n = 9) and four of these patients recalled symptoms at the time, of whom three had joint pains. Thus, in the entire group, irrespective of the trigger for diagnosis, joint symptoms had been present prior to diagnosis in 48 patients (77%) with a mean duration of 8.3 (0–45) years. The first joints reported to be affected were the MCP and the ankle followed by the knee and hip (Table 2).

At the time of clinical assessment of arthropathy, patients in group 1 had a mean duration of 6 (0.5–21) years since diagnosis of haemochromatosis. The overall

Table 2. Group 1. Prevalence of symptoms pre-diagnosis.

| Diagnostic setting | n | Symptoms pre-diagnosis, n (%) | Symptom duration pre-diagnosis (years) | First affected joint, n (%) |
|-----------------------|----|--|--|--|
| Entire group | 62 | Joint pain 48 (77) Fatigue 26 (41.9) Other 22 (35.5) None 6 (9.7) | Mean 6.8 Median 5 | MCP 17 (38.5) Ankle 13 (29.5) Knee 10 (22.5) Hips 10 (22.5) IP 7 (16) MTP 4 (9) Wrist 2 (4.5) Foot 1 (2.5) Shoulders 1 (2.5) Back 1 (2.5) |
| Symptom driven | 35 | Joint pain 32 (91) Fatigue 22 (63) Hyperpigmentation 5 (14) GI 4 (11) Other 8 (23) | Mean 8.7 Median 5 | MCP 10 (32.5) Ankle 7 (22.5) Knee 5 (16) Hips 5 (16) MTP 2 (6.5) PIP 2 (6.5) Wrist 2 (6.5) Ankle 5 (38.5) |
| Random screen | 18 | Joint pain 13 (72) Fatigue 3 (16) Other 4 (20) None 1 (5.6) | Mean 6.5 Median 6 | MCP 3 (23) Hips 3 (23) PIP/DIP 3 (23) Knee 2 (15.5) Shoulders 1 (7.5) Back 1 (7.5) MTP 1 (7.5) |
| Family history screen | 9 | Joint pain 3 Fatigue 1 Other 1 None 5 (55.5) | Mean 6.3 Median 2 | MCP 3 (100) Foot 1 (33.3) MTP 1 (33.3) Knee 1 (33.3) Hips 1 (33.3) DIP 1 (33.3) |

MCP, Metacarpophalangeal; IP, interphalangeal; PIP, proximal interphalangeal; DIP, distal interphalangeal; MTP, metatarsophalangeal; GI, gastrointestinal.

'Other' includes palpitations/depression/headache/nausea/dizziness.

prevalence of affected joints at this time is shown in Table 3 with proximal interphalangeal (PIP; 64.5%), knee (64%), ankle (61%), and MCP (60%) being the

Table 3. Distribution and prevalence of joint symptoms or signs at clinic visit (group 1) and time of completion of questionnaire (group 2).

| Region | Group 1; n = 62 Symptoms or signs (%) | Group 2; n = 470 Patient-reported symptoms (%) |
|----------|--|---|
| PIP | 64.5 | 47 |
| MCP | 60 | 46 |
| Knee | 64 | 42 |
| Ankle | 61 | 35 |
| Hip | 48 | 26 |
| DIP | 43.5 | 42 |
| Wrist | 34 | 52 |
| MTP | 30.5 | 25 |
| Shoulder | 27.5 | 20 |
| 1st CMC | 22.5 | 59 |
| Elbow | 19 | 11 |
| Mid foot | 10 | 13 |

PIP, Proximal interphalangeal; MCP, metacarpophalangeal; DIP, distal interphalangeal; MTP, metatarsophalangeal; CMC, carpometacarpal.

highest. Joint replacement surgery had been performed in 22% (n = 14), comprising 13 hips, six knees, two shoulders, and two ankles, and 16% (n = 10) had had other surgical interventions such as arthrodesis or arthroscopic treatment including ankle arthrodesis in three patients and arthroscopy in two. Orthopaedic interventions had been performed between 1 and 11 years pre-diagnosis in five patients, including ankle arthrodesis in two patients and four arthroplasties in three patients.

Group 2: UK Haemochromatosis Society member survey

The most prevalent symptoms attributed to haemochromatosis at the time of diagnosis were joint pain (76%, n = 356) and fatigue (64.5%, n = 303). Figure 1 shows the entire spectrum of symptoms reported at diagnosis, subdivided into those where the diagnosis followed symptoms (55%) and those where it arose from either random or family screening (45%). Even in the screening subgroups, where the diagnosis of haemochromatosis had not been suspected, the prevalence of symptoms at diagnosis was high, with 56%

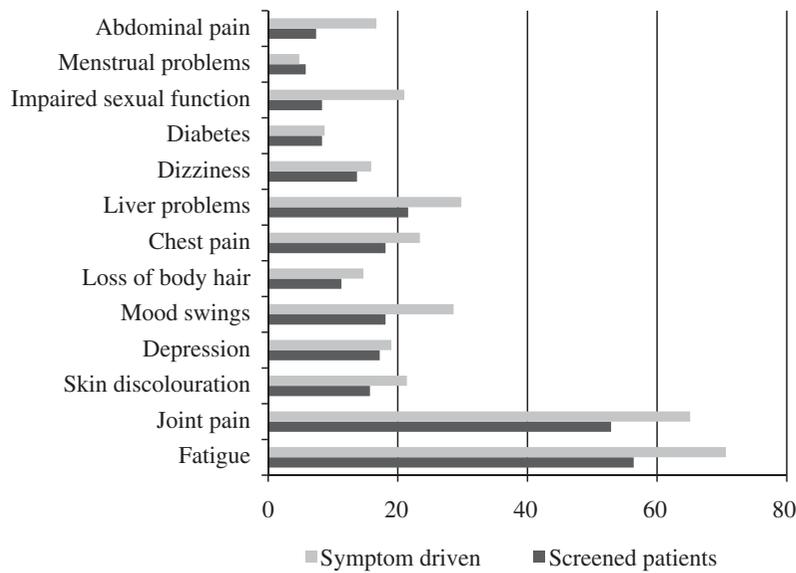


Figure 1. Group 2. Prevalence of symptoms attributed to haemochromatosis at the time of diagnosis, subdivided into those where symptoms or screening had led to diagnosis.

reporting fatigue and 53% joint pain. Figure 2 shows the timing of onset of joint symptoms in relation to the diagnosis, with 80% and 71% of patients reporting these more than 1 year prior to diagnosis in the symptom-driven and screening diagnostic groups, respectively. Table 3 shows the distribution and prevalence of joint involvement as reported by patients. Within the hand, the prevalence of involvement was very similar across the first carpometacarpal (CMC; 59%), wrist (52%), MCP (46%), PIP (47%), and distal interphalangeal (DIP; 42%) joints, and of the large joints the knee (42%) and ankle (35%) were most frequently affected. Joint replacement surgery was recorded in 23% (103/448) of respondents, with the most common

joints being the hip ($n = 44$), knee ($n = 31$), and ankle ($n = 10$).

Progress of arthropathy post-diagnosis and venesection

Joint symptoms first developed after the diagnosis of haemochromatosis in 22.5% (14/62) of patients in group 1 and 14.5% (59/404) of patients in group 2. The ferritin at diagnosis in group 1 in those with first joint symptoms pre- and post-diagnosis was 2169 $\mu\text{g/L}$ and 1473 $\mu\text{g/L}$, respectively (Mann-Whitney U test, non-significant). Venesection was reported to have had some benefit on joint symptoms by 12% of patients in

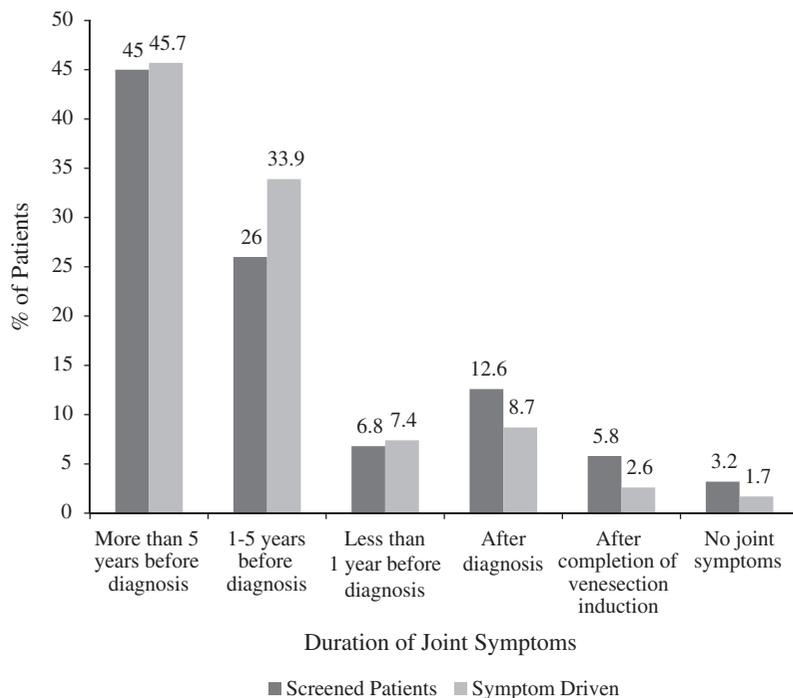


Figure 2. Group 2. Relationship between timing of onset of joint symptoms and diagnosis of haemochromatosis by screening and by symptoms.

group 1 and 5% of patients in group 2, whereas the majority of patients in both groups reported no improvement in symptoms and instead a deterioration over time, with new joints becoming affected despite maintenance of low serum ferritin concentrations.

Discussion

We report findings from two groups of patients with haemochromatosis. Group 1 comprise a population enriched for arthropathy as each patient had been referred to a specialist haemochromatosis arthropathy clinic. Patients seen in this clinic came from the locality of the hospital, and also from across the UK, as the clinic is promoted by the UK Haemochromatosis Society to its members. Therefore, this group is biased towards patients with a strong health-seeking motivation, and the more severe end of the spectrum of joint problems deemed to justify referral to a specialist clinic. Data from this group are derived from a detailed history and examination by a rheumatologist (PK). Group 2 comprises a population of patients responding to a national questionnaire developed in collaboration with and promoted by the UK Haemochromatosis Society. The data are self-reported, with no independent verification of joint symptoms. The absence of a specific marker for haemochromatosis arthropathy means that reported and observed joint problems in both groups may or may not be related to haemochromatosis.

The results from both groups are strikingly similar with a long delay between first attributable symptoms and diagnosis being confirmed, estimated by patients at a median of 5 and 4 years in groups 1 and 2, respectively. Of these symptoms, the prevalence of joint involvement at the time of diagnosis was high (group 1 77%, group 2 76%), at a mean age of 52.8 (group 1) and 56.4 years (group 2). It is noteworthy that for most patients joint symptoms had been present for a long duration, more than 1 year in 74% and 69.5%, and more than 5 years in 40% and 42.5% pre-diagnosis in groups 1 and 2, respectively. Nevertheless, these symptoms were insufficiently characteristic to prompt early diagnostic tests. Some patients had had orthopaedic interventions pre-diagnosis, without prompting diagnostic suspicion, including bilateral hip replacement surgery in one patient.

Although not all joint symptoms are necessarily related to haemochromatosis, the high prevalence and long duration of pre-diagnostic joint symptoms merits scrutiny for potential discriminatory features that might prompt diagnostic tests. The age of diagnosis in both groups was the sixth decade, with the onset of any symptoms a median of 4–5 years earlier, including joint symptoms in 76–77% in both groups. A rheumatologist might be alerted to the presentation of apparent OA at an unusually young age in the absence of family history or trauma, and hence initiate investigations; however, a non-specialist would

be less likely to appreciate this. Therefore, the distribution of affected joints is worth scrutiny. Although it is recognized that MCP joint arthropathy is a characteristic feature of haemochromatosis (6, 7), the high prevalence of involvement at all classic sites of OA in the hand (1st CMC, PIP, and DIP) is noteworthy, yet of no discriminatory value to the diagnosis of haemochromatosis. Of the large joints, the knee, ankle, and hip were most frequently found (group 1 64%, 61%, and 48%, respectively) or reported (group 2 42%, 35%, and 26%, respectively) to be involved, and in group 1 the ankle was the first joint to be affected in 29.5% of cases. In the general population, knee and hip OA are prevalent and unlikely to raise suspicion of a genetic disorder, unless an absence of family history, trauma, or the young age at presentation is taken into consideration. By contrast, OA of the ankle or hind foot is rare and this therefore has potential discriminatory value, particularly in the context of a young age and absence of foot deformity or preceding trauma.

In a series of consecutive patients presenting to an orthopaedic clinic in Iowa in 1 year, the incidence of Kellgren grade 3 or 4 OA of the knee was 66%, hip 26%, and ankle 7.5% (8). Furthermore, the majority of cases of OA hip (65%) and knee (82%) were primary in aetiology, but this only applied to 19% of ankle cases. Over 13 years, of 639 cases of Kellgren grade 3 or 4 ankle arthritis, the majority were related to trauma (69%) or known existing arthritogenic conditions such as RA, haemophilia, or neuropathy, and only 7.2% were primary. Of those with primary ankle OA, 50% had a predisposing foot deformity, leaving 3.4% (23/639) without preceding trauma, deformity, or known arthritogenic conditions. In contrast in our patients with haemochromatosis, the prevalence of ankle or hind foot arthropathy was much higher, at 61% in group 1 and 35% in group 2. Although we cannot be certain of the contribution of foot deformity, trauma, or other arthritogenic conditions among group 2, in group 1 ankle involvement was primary, and therefore of much higher prevalence than expected, and thus of discriminatory value to the recognition of haemochromatosis.

A high prevalence of ankle involvement affecting 32.9% of 199 patients with haemochromatosis has also been found by Sahinbegovic et al in an observational multicentre study (4). The enrichment of haemochromatosis in patients with ankle OA is supported by a separate study concerning the aetiology of end-stage ankle OA in 390 patients, in whom primary disease (8%) and secondary arthritic conditions (12%) were confirmed to be rare. However, haemochromatosis was recorded in nine patients (2.3%), although this may be an underestimate as it was not stated whether haemochromatosis was actively excluded in the primary cases (9). Carroll investigated 13 patients with primary OA ankle, and found haemochromatosis gene mutations in 11,

radiographic OA changes of index and middle finger MCP joints similar to haemochromatosis in seven, yet no evidence of iron overload in any cases (10). This report is striking in associating the less common *H63D* gene abnormality with phenotypic haemochromatosis arthropathy of the ankle and MCP joints, in the absence of iron overload. Similarly, the association with idiopathic hind foot arthralgia and mutations in the *HFE* gene (*C282Y* or *H63D*) has been reported in a series of 10 patients, of whom five were heterozygous for the *H63D* mutation but not iron overloaded (11). In our series, the *H63D* gene was present in five patients in group 1, yet only one had ankle arthritis.

Of note, in 22.5% patients in group 1 and 14.5% of group 2, joint symptoms first occurred after diagnosis, and in 4% of group 2 after completion of the induction phase of venesection. The onset of arthropathy at this stage, along with the report of a lack of efficacy of 'de-ironing' on joint symptoms and their progression in most patients in our series, and in other studies (4, 12), distinguishes the rheumatic manifestations from many of the other features of haemochromatosis, which generally recede with venesection. It has been proposed that sequestration of iron in the joints, as evidenced by haemosiderin staining in synovial biopsies (13), is the explanation for this; however, we have not found iron in hip and knee arthroplasty specimens from haemochromatosis patients. Further research in this area is needed, especially in the light of the finding of arthropathy typical of haemochromatosis in the absence of iron overload in cases with the *H63D* genotype (10, 11).

In summary, this survey of two UK patient groups with haemochromatosis has confirmed the long time interval between first attributable symptoms and diagnosis of haemochromatosis, with fatigue and joint pain dominating. Analysis of arthropathy reveals the MCP and ankle often to be the first affected joints, and a higher prevalence of disease at these sites than expected in patients presenting with OA in the general population. We propose that the finding of unexplained OA of the MCP or ankle joint should prompt diagnostic tests for haemochromatosis, particularly if presenting in the sixth decade or earlier, and in the absence of trauma.

Acknowledgements

We thank J. Fernau, K. Farrow, S. Fernau, C. Workman, and members of the Haemochromatosis Society for collaboration in the development, distribution, and analysis of data from the questionnaire sent to all members of the Society. This work was supported in part by the UK Haemochromatosis Society.

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