Arthropathy of haemochromatosis

Clinical and radiological analysis of 63 patients with iron overload

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Since Schumacher (1964) first suggested that the arthropathy found in two patients with idiopathic haemochromatosis might be a hitherto unrecognized complication of this disease, detailed descriptions of the joint changes have been recorded by other workers, including Delbarre (1964), de Sèze, Hubault, Welfling, Kahn, and Solnica (1964), Delbarre and Bontoux (1966), de Sèze, Ryckewaert, Hubault, Kahn, Mitrovic, and Solnica (1966), Dorfmann, Solnica, and de Sèze (1969), and Wardle and Patton (1969). We have previously reported the results of a systematic joint survey in 32 patients with idiopathic haemochromatosis, having found that sixteen of them had features of a specific arthropathy (Hamilton, Williams, Barlow, and Smith, 1968). This study has now been extended to a total of 63 patients. A more detailed analysis has been made of the radiological characteristics of the joint changes and of the relationship of these changes to the iron overload.

Patients and methods

63 patients with iron overload were studied. In each case the diagnosis of haemochromatosis had been made by clinical, biochemical, and histological criteria (Williams, 1968). Eight were seen before treatment, fifteen while treatment was in progress, and the remaining forty after completion of venesection therapy.

54 of the patients were male *propositi* with idiopathic haemochromatosis. There were four female patients with idiopathic haemochromatosis and three asymptomatic but affected male relatives. Two further patients had secondary haemochromatosis, due to hereditary spherocytosis in one and to idiopathic sideroblastic anaemia in the other.

Radiographs were taken of the hands, wrists, elbows, shoulders, pelvis, hips, knees, and feet. In 47 patients antero-posterior and lateral radiographs of the lumbar spine were also obtained.

Results

Male propositi with idiopathic haemochromatosis

An arthropathy was found on clinical examination in 31 of the 54 male patients with idiopathic haemochromatosis. The mean age at the onset of arthritic symptoms was 56 years (range 39 to 74). This excludes one patient now aged 69 who first had joint symptoms at the age of 22 years. At 35 years of age he lost libido but the diagnosis of haemochromatosis was not made until he was aged 54 years. He now has a widespread arthropathy with accompanying radiological changes.

No clear relationship was apparent between the time at which the first symptom of haemochromatosis was noted and the first symptom of arthritis. In five patients the arthritic symptoms occurred before the first symptom of haemochromatosis and in a further five patients the initial symptoms occurred together. The remaining 21 patients developed arthritic symptoms at varying intervals after the first symptom of haemochromatosis, the intervening period ranging from 1 to 24 years. Of these 21 patients, five noticed the first arthritic symptoms during the course of venesection therapy and sixteen after they had completed the planned treatment.

The age of the patient at the first symptom of haemochromatosis appears to be an important

determining factor in the development of an arthropathy (Table I). In the arthritic patients the mean age at which the first symptom of haemochromatosis was noted was 51.9 years and in the non-arthritic patients 43.4 years. The difference can also be seen by comparing the incidence of arthropathy in a group of patients in whom the first symptoms of haemochromatosis occurred when they were less than fifty years of age with those who were over 50 years old at the time of the first symptoms (Table II). Of the 28 patients who were less than 50 years of age at the time of the first symptom of haemochromatosis, 22 have been followed for at least 5 years; in that time none of these patients developed arthritic symptoms. In contrast 21 of the 35 patients who were over 50 years of age at the first symptom have been followed for the same period of time; of these patients seven developed an arthropathy.

No apparent relationship could be found between the development of an arthritis and other clinical signs of the disease such as hypogonadism or diabetes mellitus.

Clinical features

The earliest and usually the first joints to be affected by the arthritic changes were the small joints of the

hands, especially the second and third metacarpophalangeal joints. Of the 31 patients, 30 showed this type of involvement, although in some these were the only joints to be affected. Symptoms were minimal or absent at first, but the patient, on being questioned, might admit to increasing stiffness of the fingers and to occasional twinges of pain when the hands were used excessively. At this stage there was slight bony swelling and an inability to flex the metacarpophalangeal joints fully. As the arthropathy progressed, the bony swelling increased and the interphalangeal joints often became involved and the range of wrist movement restricted.

In nine patients a more generalized arthropathy affecting the larger limb joints was present. In six of these there was pain and limitation of hip movement which was sufficiently severe to warrant surgical intervention in three of them.

Superimposed on this chronic progressive joint disease, or sometimes in apparently normal joints, acute episodes of inflammatory arthritis occurred. Twelve patients in this series had such attacks, which were of varying degrees of severity. The affected joint, which was usually, but not invariably, a knee joint, became swollen, red, warm and tender, and in one instance crystals of calcium pyrophosphate

Table I *Age at onset of the first symptom of haemochromatosis in patients with and without an arthropathy and age at onset of arthritis*

Age (yrs)		< 40	40 to 49	50 to 59	60 to 69	70 or above	Mean
First symptom of haemochromatosis	Arthritic patients	9	9	4	1	0	43.4
	Non-arthritic patients	4	7	15	3	2	51.9
First symptom of arthritis		2	7	10	9	3	56.0

Table II *Comparison of incidence of arthritis in patients in whom the first symptom of haemochromatosis occurred before or after their 50 birthday*

(Patients in whom the first symptoms of arthritis occurred before the first symptom of haemochromatosis have been excluded)

Age at first symptom		Before 50th birthday	After 50th birthday
Total		28	21
No. followed for at least 5 years		22	18
*No. followed for at least 5 years who developed an arthritis	(a) within 5 years	0	7
	(b) within 5 to 10 years	2	6
	(c) within 11 to 20 years	1	2
	(d) over 20 years	4	0

* (i) Arthritis within 5 years $P < 0.002$
(ii) Arthritis within 10 years $P < 0.0001$

dihydrate were found in the joint fluid. These attacks lasted from a few days to several weeks and responded to the administration of phenylbutazone or indomethacin as well as to aspiration of the joint fluid.

Radiological appearances

HANDS

The most frequent and characteristic changes were found in the hands which were affected in the 31 patients with arthropathy. The incidence and distribution of the radiological changes were similar in the two hands but were more severe in the right (Fig. 1). The second and third metacarpophalangeal joints were almost invariably involved and the first and fourth joints much less frequently (Figs 2 and 3). The interphalangeal joints, particularly the proximal ones, were affected much less commonly and usually only mildly. The commonest and probably the earliest radiological features were small, 1 to 3 mm. diameter, well-defined cysts with sclerotic margins in the sub-articular areas of the metacarpal heads and in the base of the proximal phalanges. There was usually some loss of cartilage in almost all the joints in which cystic changes were present and this was frequently eccentric, being more severe opposite a subchondral cyst than elsewhere in the joint. Occasionally loss of cartilage was seen in the absence of subchondral cysts. In addition to the sclerosis around cysts there was frequently an ill-defined sclerosis of the whole of the metacarpal head and less often of the base of the proximal phalanx also. In contrast to this there was frequently a uniform thinning of the cortex of the metacarpals

FIG. 1 Comparison of severity and distribution of cystic changes in metacarpophalangeal joints of the two hands.

FIG. 2 Male, aged 69 yrs. Right hand, showing sclerotic changes in head of second metacarpal with loss of joint space. Less severe changes present in third metacarpophalangeal joint and at base of first metacarpal, where there are also cystic changes. Sclerosis of proximal interphalangeal joint of little finger is an unusual feature.

FIG. 3 Male, aged 60 yrs. Sclerosis, cystic changes, and loss of cartilage in third metacarpal joint of right hand. and phalanges but there was no increase in porosis near affected joints. The average thickness of the cortex at the midpoint of the second metacarpals of the 54 male propoiti was measured and compared

with the normal range for each decade established by Morgan, Spiers, Pulvertaft, and Fourman (1967). It was found that in each decade the average cortical thickness was less than expected but that there was no significant difference between those with and without arthropathy (Fig. 4). Mild chondrocalcinosis was found in the metacarpophalangeal joints of only two patients.

FIG. 4 Cortical thickness at mid-point of second metacarpal in 54 male *propositi* with haemochromatosis. Shaded area represents normal range (Morgan, Spiers, Pulvertaft, and Fourman, 1967).

WRISTS, ELBOWS, AND SHOULDERS

The carpal joints were affected in over half the patients with arthropathy. A common and prominent feature was cyst formation, usually in the lower end of the radius and ulna but also affecting the proximal carpal bones. Large cysts were usually associated with loss of cartilage, but occasionally a normal joint space was found even in association with severe cystic changes. Sclerosis was uncommon. Chondrocalcinosis was seen in the fibrocartilage of the triangular ligament in just under half the patients with arthropathy. The elbows were seldom affected (seven out of 108 joints) and always to a mild degree, usually consisting of minor cystic changes with sclerosis in two joints and loss of cartilage in only one. On the other hand, chondrocalcinosis, usually mild, was seen in twelve joints.

The shoulders were affected as often as the elbows (eight). Usually there were mild cystic changes with a little sclerosis, but in three instances there was considerable sclerosis of the subchondral bone with irregularity of the articular surface (Fig. 5). Chondrocalcinosis of the hyaline cartilage was seen in five joints and was sometimes severe.

HIPS, KNEES, AND FEET

The radiological pattern in the knees and hips was different from that in the small joints of the hands and arms. In the knees cystic changes were not seen and sclerosis was rare, but loss of cartilage was found in eighteen joints and was commonly associated with some lipping of the margins of the joints. Calcification was seen in the fibrocartilage of the menisci of thirty joints (Fig. 6), nearly twice as often as in the hyaline articular cartilage (seventeen joints).

FIG. 5 Male, aged 55 yrs. Left shoulder joint, showing sclerosis and irregularity of subchondral bone in humerus.

FIG. 6 Male, aged 55 yrs. Left knee, showing calcification in fibrocartilage of lateral meniscus and in hyaline cartilage of both femoral condyles.

Subarticular cystic changes and loss of cartilage were found in the hips of about one-third of affected patients (sixteen joints). Sclerosis was uncommon. Calcification of the articular cartilage was seen in

FIG. 7 Male, aged 69 yrs. Right hip, showing irregular calcification of acetabular labrum and joint capsule, and cystic changes in lateral margin of acetabulum.

ten joints and an occasional but striking feature was dense calcification of the fibrocartilage of the articular labrum (Fig. 7).

The feet were less commonly affected than the hands, and it was not found possible to assess the significance of the mild radiological changes in the feet.

CHONDROCALCINOSIS

This was found in sixteen of the 25 patients with arthropathy and in six with no evidence of arthropathy (average age 52.5 years (range 48 to 56), which was similar to those without either arthropathy or chondrocalcinosis). Calcification was seen in both fibrocartilage and hyaline articular cartilage. The commonest joint to be affected was the knee where

calcification in the menisci (39 out of 108 joints) was found twice as often as in hyaline articular cartilage (17 joints). The next most common site was in the wrist joint, where it was almost always confined to the fibrocartilage of the triangular ligament (21 joints). In the hip (12 joints) the calcification occurred not only in articular cartilage but also in the acetabular labrum, which caused the appearance of deepening of the joint.

Calcification was seen in the symphysis pubis in nine patients (Fig. 8) and occasionally at other sites such as in the tendo Achilles and the plantar fascia (Fig. 9).

FIG. 8 Male, aged 69 yrs. Symphysis pubis, showing dense calcification in fibrocartilage of symphysis.

Calcification was found in the intervertebral discs of seven of the 47 patients with radiographs of the lumbar spine. Amorphous calcification was seen in the nucleus pulposus as well as linear calcification

FIG. 9 Male, aged 55 yrs. Lateral view of heel, showing calcification in plantar fascia.

between the lateral margins of the vertebral bodies which has been shown to lie in the annulus fibrosis (Bywaters, Hamilton, and Williams, 1970) rather than the lateral spinal ligaments (Figs 10*a* and *b*, opposite).

Affected relatives of patients with idiopathic haemochromatosis

These three patients had no symptoms or signs and were diagnosed on systematic examination of the families. They were found to have hepatic siderosis and either a raised serum iron level or an abnormal result with the differential ferrioxamine test (Smith, Lestas, Miller, Dymock, Pitcher, and Williams, 1969). Two of these three patients were untreated at the time of the examination and the third had just completed venesection therapy. They were aged 44, 54, and 62 years, and the diagnosis had been made on average 4 years previously.

None of these patients had a clinical arthropathy although one, who was aged 54, had marked chondrocalcinosis in the menisci of both knees. No other radiological abnormalities could be demonstrated.

Female patients with idiopathic haemochromatosis

Two of these four patients had a classical poly-arthritis. The joint symptoms in these two, who were aged 80 and 59 years, had been present for 15 and 16 years respectively. In the latter patient the arthritic symptoms antedated the first symptom of haemochromatosis by 7 years, and in the other the first arthritic symptoms occurred 6 years after the first symptom of haemochromatosis. The clinical and radiological features of the arthropathy were similar to those described for the males.

Secondary haemochromatosis

Two patients with secondary iron overload were included in the survey. The first was a 76-year-old male diabetic of 4 years' standing who developed a sideroblastic anaemia of uncertain cause. Total body iron stores were increased as judged by the serum iron level and an abnormal differential ferrioxamine test. Liver biopsy showed marked iron accumulation. This patient had no joint symptoms and joint radiographs showed no abnormality.

The second (a 61-year-old male) had iron overload secondary to hereditary spherocytosis. He presented at the age of 51 years with ascites and liver failure (full clinical details of this patient were given as Case 1 of Barry, Scheuer, Sherlock, Ross, and Williams, 1968). At that time he had no joint symptoms but subsequently in 1969 he complained of stiffness and discomfort affecting the second and third metacarpophalangeal joints of both hands and of stiffness of the right shoulder joint. Joint radiographs demonstrated changes similar to those found in the male patients with idiopathic haemochromatosis, including chondrocalcinosis in the hip joints

and in one knee joint. Clinical improvement followed phenylbutazone therapy.

Discussion

In the present study 35 of the 63 patients with iron overload have evidence of an arthropathy, an incidence of 55 per cent., which is very similar to that found in our previous study in which 16 of 32 patients had an arthropathy. The incidence is the same if the male probands with idiopathic haemochromatosis are considered separately, 31 of the 54 (57 per cent.) having an arthropathy. In another large series, Dorfmann and others (1969) reported an incidence of 44 per cent. in 54 patients. It was of interest to observe a typical arthropathy in female patients with haemochromatosis and in one of the patients with a secondary haemochromatosis. Although none of the affected relatives had a clinical arthropathy one had definite chondrocalcinosis in the knees.

Six of our patients complained of joint pain or stiffness without accompanying radiological changes. However, none of the patients had radiological changes without clinical evidence of arthropathy, although three patients with both radiological and clinical features of an arthropathy had no joint symptoms whatsoever. Six patients who had never had joint symptoms and in whom the other radiological appearances were regarded as normal had prominent chondrocalcinosis; in all six the menisci were affected and in one there was also calcification of the symphysis pubis. Chondrocalcinosis is of course a recognized feature in some cases of hyperparathyroidism, and there have also been isolated case reports in ochronosis, Wilson's disease, and hypophosphatasia. The significance of its association with other metabolic disorders such as diabetes and gout is, as yet, uncertain. We do know that it can occur in the absence of any apparent metabolic defect, and Atkins, McIvor, Smith, Hamilton, and Williams (1970) have demonstrated normal iron metabolism in sixteen patients with idiopathic chondrocalcinosis.

The similarity to rheumatoid arthritis lies in the distribution of the joint disease in the hand, the most severe lesions occurring in the second and third metacarpophalangeal joints. However, there is a tendency to sclerosis in the neighbourhood of affected joints rather than osteoporosis, marginal erosions are uncommon and when present result from infraction of a cyst rather than erosion from outside the bone. Ulnar deviation is not a feature. The radiological changes in the hips and knees may be indistinguishable from osteoarthritis with sclerosis, loss of cartilage, and marginal lipping. There is a superficial similarity to ankylosing spondylitis, but in haemochromatosis the calcification is in the lateral margins of the intervertebral discs rather than the

FIG. 10 *Male, aged 69 yrs. Lumbar spine, showing (a) calcification in lateral margins of intervertebral discs, and (b) calcification in anterior and posterior margins of intervertebral discs at several levels and of the nucleus pulposus between lumbar 1 and lumbar 2.*

lateral ligaments of the spine (Bywaters and others, 1970).

The findings of Hamilton and others (1968) that these patients whose first symptoms of haemochromatosis occurred after 50 years of age were more liable to develop an arthritis has been confirmed in this series and shown to be highly significant. This is probably not an indication of a different type of haemochromatosis at these ages but is more likely to be due to an additional effect of age. Both an older age and iron overload are important determining factors in the arthropathy.

The aetiology of the arthropathy of haemochromatosis in patients with iron overload is quite unknown. It is tempting to suggest that it is due to iron deposition in the joint tissues, and Sheldon (1935) noted haemosiderin deposits in the articular cartilage and synovium of patients with haemochromatosis, a finding which has been confirmed in synovial biopsy material by Dymock, Ansell, Atkins, Hamilton, and Williams (1970). The finding of a similar arthropathy in our patient with secondary iron overload would be evidence that iron overload may be the initiating factor. However, the arthritic symptoms may occur for the first time after completion of venesection therapy.

Under normal conditions pyrophosphate is hydrolysed to a soluble orthophosphate by the pyrophosphatase enzyme activity present in cartilage (McCarty, Hogan, Gatter, and Grossman, 1966). A failure or inhibition of this enzyme activity could therefore lead to calcium pyrophosphate deposition, but whether this is so has yet to be determined. Other

factors, however, must be involved, for Atkins and others (1970) have shown that the pattern of the arthritis in idiopathic chondrocalcinosis differs from that in haemochromatosis. A study of the subchondral bone may therefore lead to important clues to the nature of the arthropathy.

Summary

In a survey of 63 patients with iron overload, 35 (55 per cent.) had radiological or clinical evidence of an arthropathy. The incidence in 54 male probands with idiopathic haemochromatosis was 57 per cent. Two of four female patients with idiopathic haemochromatosis and one of the two with a secondary haemochromatosis also had an arthropathy. The arthritis was more common in the patients whose first symptom of iron overload occurred after their 50th birthday. Age and iron overload appeared to be the main causative factors in this group of patients, but venesection therapy did not influence the arthropathy.

The radiological features seen in these patients were cystic changes and sclerosis in the subchondral bone, loss of articular cartilage, and chondrocalcinosis of the articular cartilage. Six patients had chondrocalcinosis without either an arthropathy or other radiological abnormalities.

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References

- ATKINS, C. J., MCIVOR, J., SMITH, P. M., HAMILTON, E., AND WILLIAMS, R. (1970) *Quart. J. Med.*, **39**, 71 (Chondrocalcinosis and arthropathy: Studies in haemochromatosis and in idiopathic chondrocalcinosis).
- BARRY, M., SCHEUER, P. J., SHERLOCK, S., ROSS, C. F., AND WILLIAMS, R. (1968) *Lancet*, **2**, 481 (Hereditary spherocytosis with secondary haemochromatosis).
- BYWATERS, E., HAMILTON, E., AND WILLIAMS, R. (1970). In preparation. (The spine in idiopathic haemochromatosis).
- DELBARRE, F. (1964) *Presse méd.*, **72**, 2973 (Les manifestations ostéo-articulaires de l'hémochromatose).
- AND BONToux, D. (1966) *Bull. Soc. méd. Hôp. Paris*, **117**, 881 (Signes et complications ostéo-articulaires de l'hémochromatose).
- DORFMANN, H., SOLNICA, J., AND SÈZE, S. de (1969) 'XII Congressus Rheumatologicus Internationalis'. In press (Résultats d'une recherche prospective des arthropathies chez 54 hémochromatosiques).
- DYMOCK, I. W., ANSELL, I. D., ATKINS, C. J., HAMILTON, E., AND WILLIAMS, R. (1970). In preparation (Synovial biopsy in haemochromatosis).
- HAMILTON, E., WILLIAMS, R., BARLOW, K. A., AND SMITH, P. M. (1968) *Quart. J. Med.*, n.s. **37**, 171 (The arthropathy of idiopathic haemochromatosis).
- MCCARTY, D. J., HOGAN, J. M., GATTER, R. A., AND GROSSMAN, M. (1966) *J. Bone Jt Surg.*, **48-A**, 309 (Studies on pathological calcifications in human cartilage. I. Prevalence and types of crystal deposits in the menisci of 215 cadavera).
- RGAN, D. B., SPIERS, F. W., PULVERTAFT, C. N., AND FOURMAN, P. (1967) *Clin. Radiol.*, **18**, 101 (The amount of bone in the metacarpal and the phalanx according to age and sex).
- SCHUMACHER, H. R. (1964) *Arthr. and Rheum.*, **7**, 41 (Haemochromatosis and arthritis).
- SÈZE, S. DE, HUBAULT, A., WELFLING, J., KAHN, M. F., AND SOLNICA, J. (1964) *Rev. Rhum.*, **31**, 479 (Les arthropathies des hémochromatoses).
- , RYCKEWAERT, A., HUBAULT, A., KAHN, M. F., MITROVIC, D., AND SOLNICA, J. (1966) *Sem. Hôp. Paris*, **42**, 2461 (Les chondrocalcinose articulaires).
- SHELDON, J. H., (1935) 'Haemochromatosis'. Oxford University Press, London.
- SMITH, P. M., LESTAS, A. N., MILLER, J. P. G., DYMOCK, I. W., PITCHER, C. S., AND WILLIAMS, R. (1969) *Lancet*, **2**, 402 (The differential ferrioxamine test in the management of idiopathic haemochromatosis).
- WARDLE, E. N., AND PATTON, J. T. (1969) *Ann. rheum. Dis.*, **28**, 15 (Bone and joint changes in haemochromatosis).
- WILLIAMS, R. (1968) 'Iron Metabolism' in 'Recent Advances in Medicine', ed. D. N. Baron, N. Compston, and A. M. Dawson, p. 170. Churchill, London.