The spine in idiopathic haemochromatosis

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The development of a specific arthropathy is now a well recognized complication of idiopathic haemochromatosis (Schumacher, 1964; de Sèze, Hubault, Kahn, Welfling, Jaffres, Mitrovic, and Solnica, 1966; Hamilton, Williams, Barlow, and Smith, 1968); one of the characteristic features found in the majority of affected joints is the presence of calcium pyrophosphate deposits in both hyaline and fibrocartilage. Further studies have shown a direct, but not necessarily causal, relationship between hyaline cartilage calcification and the joint damage (Atkins, McIver, Smith, Hamilton, and Williams, 1970). Chondrocalcinosis due to calcium pyrophosphate deposition, in the absence of other disease, was first described by McCarty, Kohn, and Faires (1962) and by Žitňan and Sit'aj (1963). Sit'aj and Žitňan (1967) also reported calcification of the cervical and lumbar intervertebral discs in a long term study of 39 patients, some of whom gradually developed stiffening of the spine. Calcification of intervertebral discs is sometimes found in hyperparathyroidism, where chondrocalcinosis of peripheral joints has been described (Bywaters, 1959; Zvaifler, Reefe, and Black, 1962; Bywaters, Dixon, and Scott, 1963), and for many years disc calcification has also been known to occur in ochronosis.

During the period of the present study, six patients with haemochromatosis have come to autopsy, and this paper describes the radiographic, macroscopic, and histological changes found in their lumbar spines, together with the appearances using polarized light microscopy. In addition, radiography of the lumbar spine has been undertaken in 47 patients with idiopathic haemochromatosis and the results are compared with the incidence of disc calcification in a general population.

Results

In seven (15 per cent.) of the 47 living patients with idiopathic haemochromatosis, calcification of one or more of the intervertebral discs was clearly visible radiographically (Fig. 1).

All of these seven patients had arthropathy and

FIG. 1 Case 6. Antero-posterior radiograph of lumbar spine, January 5, 1961.

chondrocalcinosis in peripheral joints. Any of the lumbar intervertebral discs could be involved

except L5-S1. The radiographic appearances in an antero-posterior view could closely resemble the peripheral disc ossification seen in ankylosing spondylitis, but sometimes in addition the nucleus of the disc was also calcified. The incidence of disc calcification in the lumbar spine in an unselected series of straight antero-posterior x rays taken in male patients matched for age before an intravenous pyelogram was also recorded. One hundred films were examined, and in six disc calcification was seen, but in each case the changes were minimal, and were confined to the margin of one interspace.

The clinical details of the six patients who came to autopsy are shown in Table I. There were four men and two women whose ages ranged from 68 to 80 yrs. All but one were diabetic. Three had been depleted of iron by multiple venesections. Five patients had a peripheral polyarthritis with widespread chondrocalcinosis in four. The mean duration of their joint symptoms was 12.6 yrs (range 2 to 18). Two were severely disabled but in none had pain or stiffness of the spine been prominent symptoms. Episodes of acute arthritis occurred in one patient and, although crystals of calcium pyrophosphate were not demonstrated in joint fluid during life, they were subsequently shown to be present in the menisci of the knee joints using x-ray diffraction crystallography.

PATHOLOGICAL FINDINGS

Lumbar spine specimens from these six cases varied from three to seven vertebral bodies and included *ligamentum flavum* in four instances (Table II, opposite).

While discoloration and degeneration of some or all of the intervertebral discs was seen in four cases, it was almost absent in two (Cases 2 and 6). As may be seen by reference to Table II, there was no individual correlation of disc degeneration with presence of peripheral arthropathy or chondrocalcinosis, duration of joint symptoms, or therapeutic iron removal. Although most disc degeneration was seen in the two eldest patients and least in the youngest, there was only 12 years difference between them in age at death. No gross disc degeneration was seen in Case 6, an iron depleted patient with widespread clinical arthropathy and crystal deposition; minimal change only was seen in one disc of Case 2.

In others, degeneration affected 2/7 discs (Case 3, Fig. 2, opposite), 2/6 discs (Case 1), 1/4 discs (Case 5), in varying degree. Prussian blue staining for iron in disc cartilage was negative. The sixth subject (Case 4) showed discoloration and fissuring without collapse in 3/4 discs (Fig. 3, overleaf) and collapse in the 4th disc. In this case and in two others showing the more severe disc degeneration, there was damage to the vertebral plates with break-up of the plate (at L5-S1 in Case 4 and at L4-5 in Case 3, Fig. 2). In the third subject (Case 1), vertebral body collapse had occurred on the upper segment of L2 and L3, without plate disruption (Fig. 4, overleaf) but degenerative changes were present in L1-2 and L4-5 discs without plate damage. The degenerative changes in the discs leading to fissuring and cavitation did not seem different (with the exception of crystal deposition) from that seen in control material

Table I *Clinical details in six autopsied cases*

Case no.	Sex	Age (yrs)			Haemochromatosis		Joints		
		First symptom	Diagnosis	Death	Diabetes	Iron removed (g.)	Arthropathy	Chondrocalcinosis	Duration of symptoms (to death) (yrs)
1	M	75	75	79*	—	0	Hands	Hands, wrists, hips, knees	2
2	M	70	70	71*	+	0	Hands	None	10
3	F	68	71	73*	+	3.7	None†	None	—
4	F	45	73	80	+	3.6	Hands, elbows, knees, ankles	Widespread in hyaline and fibrocartilage	18
5	M	55	69	71*	+	0	Widespread polyarthritis	Widespread in hyaline and fibrocartilage	16
6	M	52	55	68*	+	19	Widespread† polyarthritis	Widespread in hyaline and fibrocartilage	17

* Neoplasm present † Iron absent in synovial membrane

Table II *Pathological findings in lumbar spine of six autopsied cases*

Case no.	Sex	Segments	Discs	Ligamentum flavum	Vertebral plate
1	M	L1-5	Degeneration L1-2 and L4-5 CALCIFIC mainly in these two discs	CALCIFIC	Collapse upper surface L2 and L3
2	M	L1-S1	Normal (Minimal degeneration L5-1)	—	Normal
3	F	T12-S1	Degeneration L4-5 with protrusion of L5-1	0	Collapse upper surface L1 body L4-5 and 5-1 damaged
4	F	L2-S1	Severe degeneration and discoloration with degenerative thinning of L5-1 CALCIFIC	—	Break-up L5-S1 L3 lower face, sagittal L5 upper face, coronal
5	M	L1-5	Slight degeneration L12, L5-S1, and protrusion L3-4 Others intact CALCIFIC	CALCIFIC	Normal
6	M	L3-5	No degeneration Normal height CALCIFIC	CALCIFIC	Normal

FIG. 2 *Case 3. Sagittal section. T 12-S1 shows minimal degeneration except in L4-5, L5-S1 but no calcification.*

of the same age. In Case 4 at the age of 80, there were marked degenerative changes at L5-S1, with discoloration and plate break-up (Fig. 5, overleaf). The marrow spaces were filled with regenerated cartilage. It is interesting that the x-ray appearances of the chondro-osseous junction resemble those characteristic changes in the peripheral joints of haemochromatosis; such juxta discal bone changes were uncommon here, however, both in individual vertebrae and in individuals. Case 3 also showed

collapse of the upper surface of L1 without vertebral plate damage not, apparently, due to metastases. Crystal deposition was seen in the discs in 4/6 cases and in *ligamenta flava* in the same cases. Calcification occurred in some discs and not in others, corresponding in Cases 4 and 6 to that seen radiologically during life. The crystals of calcium pyrophosphate dihydrate, identified by their shape and their positive birefringence (and by x-ray diffraction in Case 6) were laid down along the lines

FIG. 3 Case 4. Sagittal section. L1-5 shows gross discoloration and degenerative changes, and break-up at L4-5; minimal calcification on x ray.

FIG. 4 Case 1. Sagittal and coronal sections, showing collapse of upper surfaces of L2 and L3. Moderate calcification.

FIG. 5 Case 4. L5-1, showing break-up of the subchondral cartilaginous plate, more marked on one side than the other, with protrusion of the disc. Haematoxylin and eosin. $\times 6$.

of the outer annular fibres (Fig. 6), usually in clearly defined elongated globular masses (Fig. 7).

FIG. 6 Case 6. Sagittal section L3-4-5, showing crystal deposition.

They were seen most clearly peripherally in discs without degenerative changes: when, however, there were degenerative changes the crystal masses were deposited along the margins of the slit-like fissure (Fig. 8). This occurred even in the minimal fissuring seen microscopically without gross deposition in Case 6 (Fig. 9, overleaf).

FIG. 7 Case 6. Undecalcified lumbar disc by polarized light. Haematoxylin and eosin. $\times 20$.

These crystal masses did not occur in the neigh-

FIG. 8 Case 5. L5-S1, showing crystal deposition in margins of fissure. Haematoxylin and eosin. $\times 15$.

FIG. 9 Case 6. L2-3 undecalcified, showing deposition in margins of minimal fissuring. Haematoxylin and eosin. $\times 20$.

bourhood of chondrocytes or in the nests of hypertrophied and proliferating chondrocytes, which were

FIG. 10 Case 4. Crystal deposition in fissure margins avoiding chondrocyte nests. Haematoxylin and eosin. $\times 66$.

often surrounded by a clear space of ground substance (Fig. 10). Nor did they occur on the collagen fibres where these had become visible. Small and

FIG. 11 Case 1. Undecalcified, showing crystal deposits near vacuoles. Haematoxylin and eosin. $\times 150$.

hence apparently early deposits were seen in the neighbourhood of the basophil fluid accumulations that occur as fissuring develops in the fibrocartilaginous matrix (Fig. 11). These balloon-like spaces containing a delicate foamy structure staining blue with haematoxylin are surrounded and defined by the remains of the matrix. It is in the latter that the characteristic pyrophosphate crystals are deposited (Fig. 12a, b, and c), at first sparingly with fairly

large crystals, then more densely packed and small. In calcified sections stained with haematoxylin and eosin the matrix in which pyrophosphate had previously been embedded is clearly recognizable as a dark purple haematoxylin staining granular mass in which it is often possible to see the outlines of the dissolved crystals. The crystal deposits occurred in the degenerate discs along the margins of the fissure, sometimes superficially and sometimes just

(a)

FIG. 12 (a) Case 1.
Haematoxylin
and eosin.
× 100.
(b) The same,
polarized light.
(c) overleaf

(b)

(c)

FIG. 12 (c) *Higher magnification of area outlined in (a), showing crystals. $\times 400$.*

FIG. 13 *Case 5. Sagittal section. L3-4. Haematoxylin and eosin. $\times 7.5$.*

beneath the surface, not only in the annular region but also in the region occupied previously by the nucleus pulposus where the fibrocartilage matrix was cut across at right angles to its fibres, themselves showing fraying and fissuring (Fig. 13). Crystal deposits occurred here just below the frayed surface and again avoided the area around the chondrocytes.

In the *ligamentum flavum*, crystal deposits were seen as large mulberry-like masses pushing aside the

elastic fibres (Fig. 14), and as smaller ('earlier') accumulations appearing to develop in unaltered tissue. Occasionally a small area with basophil granular change enveloping the elastic fibres was seen in proximity to the crystal deposits, but itself contained no crystals. *X-ray* of these 3.5 mm. slices shows them to string out along the line of the fibres as streaks (Fig. 15) and as a thin cloud of dust (Fig. 16, overleaf).

FIG. 14. Case 5. L2-3, ligamentum flavum showing pyrophosphate deposits. Haematoxylin and eosin. $\times 40$.

FIG. 15 Case 6. Sagittal section L3-4, showing deposition in ligamentum flavum, gross (right) and on x ray (left).

Discussion

In idiopathic haemochromatosis, calcium pyrophosphate deposition in the spine is confined to the discs and ligamentum flavum and, although in certain radiographic views there can be a superficial resemblance to ankylosing spondylitis, it differs from

ankylosing spondylitis in the nature and site of the calcification, the absence of inflammatory changes, and the fact that it is not accompanied by stiffness and limitation of back movement.

Similar and more extensive spinal calcification involving the cervical and lumbar discs has been

FIG. 16 Case 5. Lateral sagittal section. X ray showing deposits in ligamentum flavum, T12-L3.

FIG. 17 Intervertebral disc from cervical spine of a man with hyperparathyroidism (Case IV of Bywaters, Dixon, and Scott, 1963), by polarized light, showing pyrophosphate crystals deposited along fissures in the fibrocartilage. Haematoxylin and eosin. $\times 40$.

reported in idiopathic chondrocalcinosis by Žitňan and Sit'aj (1966). Their patients, in whom there was a strong familial incidence of chondrocalcinosis, frequently developed disc calcification by the third decade, and afterwards there was progressive spinal stiffness. Disc calcification can also occur in hyperparathyroidism (Bywaters, Dixon, and Scott, 1963) and here has been shown to be due to calcium pyrophosphate deposition (Bywaters, 1969; unpublished data). As in the present instances, crystal deposits appeared to occur in relation to fissure spaces (Fig. 17). This contrasts with ochronosis, in which calcium apatite is found in the discs, but both calcium pyrophosphate and apatite have been identified in a synovial joint (Bywaters,

Dorling, and Sutor, 1970). Widespread disc degeneration is a prominent feature in ochronosis, but in haemochromatosis the degenerative changes were not more than to be expected in the age group involved. Crystal deposition could occur in the absence of gross change in the disc, although its occurrence adjacent to fissures may be of significance. Crystal deposition depends on adequate ionic concentrations and the absence of pyrophosphatase—excluded from avascular cartilage with other large molecules (Laurent, 1966), but its deposition in fissures suggests that in addition to such factors there may be a facilitating factor, perhaps change in macromolecular concentration, in these degenerative spaces.

It should be stressed that the changes described have so far not been shown to cause symptoms, and that they were only found in patients in whom there was peripheral arthropathy and chondrocalcinosis. There is no evidence that either the spinal changes or the peripheral arthropathy have been influenced by reducing the iron overload by venesection therapy.

Summary

Calcium pyrophosphate deposition occurred in the *ligamentum flavum* and in the peripheral parts and fissure surfaces of the intervertebral discs in four of six patients with idiopathic haemochromatosis. In one, the λ ray *in vivo* resembled that of ankylosing

spondylitis, with pseudosyndesmophytes, and histological studies revealed deposition of calcium pyrophosphate crystals in the outer and peripheral layers of the annulus fibrosus. In other cases in which disc degeneration had occurred, deposits were localized to the immediate neighbourhood of the fissures. Even in the earliest phases, pyrophosphate deposition seems to be associated with microfissure formation and the accumulation of mucopolysaccharide in between collagen bundles. It did not seem to be related except geographically to disc degeneration, and the appearances were the same in the untreated case and in those who had had multiple venesections. No iron staining was seen in disc cartilage.

APPENDIX

Case histories

CASE 1. This man was 75 years in 1964 when a diagnosis of cirrhosis was made following haemorrhage after a tooth extraction. In November, 1966, he had haematemesis from oesophageal varices. On examination then he was generally pigmented with scanty body hair, small soft testes, and hepato- and splenomegaly. The serum iron was raised to 190 $\mu\text{g./100 ml.}$ with a total iron-binding capacity of 230 $\mu\text{g./100 ml.}$ A glucose tolerance test gave a fasting blood sugar of 64 mg./100 ml. rising to 136 mg./100 ml. at 1 hour and falling to 128 mg./100 ml. at 2½ hours. A liver biopsy showed cirrhosis with Grade IV iron deposition. There was no family history of haemochromatosis.

In view of his age it was decided not to undertake multiple venesections; he remained reasonably well for a few months until April, 1967, when he was readmitted with a urinary tract infection and uraemia. On this admission he was noted to have arthritis of several MCP joints, and the radiographs showed chondrocalcinosis in his hands, wrists, hips, and knees. He was discharged after treatment of his urinary infection but later that year had a further haematemesis from which he died at the age of 79.

Autopsy showed a ruptured oesophageal varix. The liver was cirrhotic and showed numerous nodules, the histological appearances of which were those of a well-differentiated hepatoma; the liver showed Grade IV iron deposition and the characteristic appearances of haemochromatosis. The knee joint showed synovial iron deposition chondrocalcinosis but no arthropathy.

CASE 2. The first clinical manifestation of haemochromatosis in this man was diabetes which was diagnosed at the age of 70 in 1967 and treated successfully with chlorpropamide (250 mg. daily). In 1968 he developed temporal arteritis which responded to prednisone but later that year he was referred to King's College Hospital because of hepatomegaly and ascites. He gave a history of low back pain for 3 months and more recently abdominal swelling with severe epigastric pain. For about 10 years he had had occasional rheumatic pains in several joints.

On admission in September, 1968, he was thin and

pigmented, with ascites and an enlarged liver palpable 10 cm. below the costal margin. The serum iron was 125 $\mu\text{g./100 ml.}$ and total iron-binding capacity 155 $\mu\text{g./100 ml.}$ Liver function was abnormal.

Minor osteophytic lesions were seen in the lumbar spine and knees. In the hands there was loss of cartilage in the second left MCP joint with a few small cystic changes in the interphalangeal joints. Synovial biopsy showed slight reduplication of synovial lining cells which contained considerable haemosiderin. The connective tissue showed no increase of chronic inflammatory cells, but there were a number of haemosiderin-laden macrophages. Crystals from the joint fluid had the characteristics of calcium pyrophosphate.

A liver scan revealed a filling defect in the left lobe corresponding to the palpable epigastric nodule, and a biopsy from this area showed an anaplastic carcinoma. This condition deteriorated rapidly and he died in October, 1968, the final cause of death being bleeding from oesophageal varices. At autopsy the liver showed a micronodular cirrhosis, with Grade IV iron deposition and the characteristic histological appearances of haemochromatosis. Approximately three-fifths of the left lobe were replaced by a well-differentiated hepatoma. The knee joint was normal apart from synovial iron deposition. No calcification was visible in the spinal segment removed.

CASE 3. This woman had developed diabetes at the age of 68 in 1963, which was controlled on chlorpropamide. In 1966, after a history of indigestion for 18 months, her gall bladder was removed and showed a small tumour at the fundus, histologically a poorly-differentiated adenocarcinoma. At the time of surgery the liver was noted to be nodular, and a liver biopsy showed a micronodular cirrhosis with Grade IV siderosis.

Subsequent investigations in 1967, at the age of 72, showed a raised serum iron of 215 $\mu\text{g./100 ml.}$ and a total iron-binding capacity of 240 $\mu\text{g./100 ml.}$ She was pigmented with sparse body hair and the liver was enlarged 6 cm. below the costal margin. She had no joint symptoms and her joints were clinically and radiologically normal. There was no family history of haemochromatosis or of

diabetes.

She was then treated by multiple venesections and 3.7 g. iron were removed. In March, 1968, she was readmitted complaining of upper abdominal pain of 2 months' duration and the loss of 14 lb. in weight. The liver was larger than previously with a hard nodule in the lower edge. Her condition slowly deteriorated and she died in November, 1968.

At autopsy white hard tumour tissue extended from the bed of the gall bladder into the liver. The histological appearances were those of a poorly-differentiated adenocarcinoma similar to the primary tumour. Otherwise, the liver showed a micronodular cirrhosis with some iron still present in the parenchymal cells (Grade I). Examination of the right knee joint showed slight irregularity of the medial surfaces of the patella and of both condyles, but no calcification of the articular or meniscal cartilages could be detected. Iron stains of the synovial tissue were negative. The MCP joint of the left index finger was also normal.

CASE 4. This woman had had diabetes since 1932 and had been taking insulin since 1943. In 1959, at the age of 71, she noticed brown pigmentation of the skin of her feet and arms. On examination in 1960 the liver was found to be enlarged. The serum iron was 246 $\mu\text{g.}/100\text{ ml.}$ and total iron-binding capacity 303 $\mu\text{g.}/100\text{ ml.}$ A liver biopsy showed septal fibrosis with early nodule formation. The portal tracts contained a mixed inflammatory cell infiltrate and there was Grade IV siderosis. Her mother and one aunt had diabetes and two of her sons on subsequent investigation proved to have hepatic siderosis with a raised serum iron level. She was treated by multiple venesections and between February and August, 1961, 3.6 g. iron were removed.

She attended sporadically and remained reasonably well until April 28, 1967, when she developed an acute arthritis of the right elbow. 5 ml. of fluid were aspirated; this contained no crystals. On direct questioning she admitted to episodes of acute arthritis in her knees and left hand, and that she had had an acute arthritis of the right elbow some 18 years earlier. A skeletal x-ray survey showed chondrocalcinosis in the hips, knees, and ankles, in the left shoulder, and in the fibro-cartilage of the symphysis pubis and the triangular ligament of the wrist. The following year, in August, 1968, she was readmitted with diabetic precoma after a urinary tract infection. She recovered only to collapse suddenly and died on the 8th day after admission with a massive pulmonary embolus.

At autopsy the liver showed portal fibrosis with some bridging in the portal tracts and mild chronic inflammatory infiltration in the portal areas. The knee and hip joints showed gross chondrocalcinosis and there was a severe arthritis of the right elbow joint. The liver and joints showed no iron deposition.

CASE 5. This man had developed diabetes in 1952 and soon afterwards arthritis in his hands and feet. His knees and hips were subsequently involved and he became progressively disabled despite intensive physiotherapy and courses of gold, indomethacin, and phenylbutazone. In 1965 a cup was inserted into the right hip joint which had to be removed 5 weeks later because of infection. Since then he has been able to walk only

slowly. Hepatomegaly and pigmentation were first noted in 1966. There was no family history of diabetes or cirrhosis, but one brother was subsequently found to have a raised serum iron and hepatic siderosis.

On admission to King's College Hospital in December, 1967, at the age of 70, he was pigmented and the liver was enlarged 10 cm. Body hair and testes were normal. Biopsy showed cirrhosis with Grade IV iron deposition. He was severely crippled. There was bony swelling of the MCP and PIP joints but no ulnar deviation. Both hip joints were severely restricted, the elbows lacked 10° of full extension, and there was crepitus and bony swelling of the knees without effusion.

Synovial biopsy of the knee showed moderate villous hyperplasia and iron deposition in synovial lining cells and subjacent macrophages. Radiographs showed severe arthritis of the second and third MCP joints of both hands as well as both hip joints, and there was widespread chondrocalcinosis which involved both the hyaline and the fibro-cartilage.

Ring arthroplasty of the right hip performed in February, 1968, gave some relief, but on May 16, 1968, he was readmitted with increasingly severe pain in the joints, abdominal pain, fever, and loss of weight. A liver scan showed a filling defect suggestive of a hepatoma. He died on August 8, 1968. Autopsy showed a well-differentiated hepatoma and the typical appearances of untreated idiopathic haemochromatosis. Joints showed arthropathy, chondrocalcinosis, and synovial iron deposition.

CASE 6. A bank cashier, aged 55 came to King's College Hospital in 1954, giving a 3-year history of general ill-health with more recent polyuria and polydipsia. On examination he was markedly pigmented with hepatomegaly and testicular atrophy, the diagnosis of haemochromatosis being later confirmed by liver biopsy. From August, 1957, to May, 1961, 19 g. iron were removed by multiple venesections. With this he improved and the pigmentation and hepatomegaly became less marked though there was no change in the hypogonadism or insulin requirements. In 1966 his health deteriorated and in November, after several haematemeses, he was admitted to St. Bartholomew's Hospital and died on February 26, 1967. Autopsy showed a large hepatoma; the joints showed arthropathy and chondrocalcinosis but were iron-free.

The arthritis had first appeared in both knees in 1950 and later spread to involve his hands, wrists, hips, ankles, and feet. Rheumatoid arthritis was diagnosed and in 1959 he was given a short course of prednisone with no appreciable benefit. In 1960 there was swelling of the small joints of the hands and limited abduction of both hip joints, and the knees and ankles were swollen. X rays demonstrated the presence of articular chondrocalcinosis. Since then he had become progressively disabled by the arthritis in his hips and knees, and could walk only with great difficulty.

Examination in 1967 showed obvious bony swelling of the interphalangeal and MCP joints. There was no ulnar deviation of the fingers or tendon involvement. Movements of the wrists were limited, abduction and rotation were severely restricted in both hip joints, and there was bony swelling of the knees with restriction of full flexion. The ankle joints were markedly limited and the subtalar joints fixed.

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