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Pyrophosphate arthropathy: a clinical and radiological study of 105 cases*

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SUMMARY 105 consecutive patients who presented to a rheumatologist because of joint disease and who also had evidence of deposition of calcium pyrophosphate dihydrate (CPD) were studied clinically and radiologically. There were 76 women (mean age 73) and 29 men (mean age 62). Of only 18 patients below the age of 60 at presentation 12 were men. The majority of the younger male group suffered from acute attacks of synovitis, and had no clinical or radiological evidence of joint damage. In contrast the older female group had widespread destructive changes. Associated joint disease included generalised osteoarthritis (45), rheumatoid arthritis (8), joint hypermobility (13), previous knee surgery (8), and gout (2). Sixteen patients had received long-term steroid therapy. Severe destructive joint changes were seen in 16 patients. The radiological features in those with rheumatoid arthritis by ARA criteria were atypical. The relationship between CPD deposition and arthritis is discussed in the light of these findings.

The deposition of calcium pyrophosphate dihydrate (CPD) in articular cartilage is a common, well described phenomenon, which has a characteristic distribution and radiological features including chondrocalcinosis.[1]

Several clinical syndromes are thought to be caused by the presence of pyrophosphate crystals in the articular cartilage, synovium, or synovial fluid.[2 3] However, many patients with radiological chondrocalcinosis are asymptomatic,[2 3] which casts doubt on the role of these crystals as a cause of joint damage.[4]

There have been relatively few clinical surveys of patients with chondrocalcinosis, and most have included only small numbers of selected patients. In an attempt to elucidate the relationship of pyrophosphate deposition and joint disease a large, unselected population of patients has been studied both clinically and radiologically.

Patients and methods

105 consecutive patients presenting to a rheumatologist because of joint disease, associated with radiological and/or microscopic evidence of pyrophosphate deposition, were studied. The criteria for inclusion were radiological linear shadows of calcific density within hyaline or fibrocartilage[1 5] and the presence of typical monoclinic or triclinic, positively birefringent crystals in synovial fluid or tissue specimens.[6 7]

A full medical history was recorded on all patients. Particular attention was given to a family history of arthritis, any past or present medical or surgical conditions that might predispose to pyrophosphate deposition,[8] and the drug history. The number, site, and duration of any acute attack of arthritis were recorded and the time of onset and site of chronic symptoms noted. The joints were examined for evidence of disease at the time of the survey. Particular attention was paid to the knees, where effusions, crepitus, and severity of involvement were scored on a 0–3 scale (none, mild, moderate, severe). Individual joints of the hand were examined, and evidence of joint damage was charted on a similar 0–3 scale. Hypermobility was scored by the method of Carter and Wilkinson, modified by Beighton *et al.*[9] *X*-rays were taken of hands, wrists, thoracolumbar spine, pelvis, and other clinically involved joints, and these were examined for evidence of chondrocalcinosis and joint disease.

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Synovial fluid was examined by conventional polarised light microscopy. Biopsy material was available from 5 patients whose knees were examined by arthroscopy. The samples were fixed and stained at neutral pH for conventional histological examination, and also examined under polarised light.

Results

The diagnosis of pyrophosphate deposition was based on the presence of typical radiological features alone in 73 patients, on radiological features plus synovial fluid or tissue crystals in 28, on synovial fluid findings alone in 3 patients, and on biopsy alone in one case. Only 4 patients had no radiological evidence of chondrocalcinosis.

CLINICAL FEATURES

Of the 105 patients 29 were men (mean age 62) and 76 women (mean age 73), a male:female ratio of 0·38. Only 18 patients were under 60 at the time of presentation, and of those 12 were men, a male:female ratio of 2·0 (Fig. 1).

The earliest symptoms of joint disease were in the knee joint (Table 1). Lower limb involvement (knee and ankle) was more common at presentation in men (82%) than women (53%). The women had a wider spectrum, of presenting symptoms and joint involvement and also gave a longer history of joint symptoms (mean 13 years) than men (mean 10 years).

Table 1 *Distribution of joint involvement in patients with pyrophosphate arthropathy (expressed as a percentage)*

Joint	*Overall involvement*		*First joint involved*		*Most troublesome joint*	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
Knee	92·8	92·0	71·0	48·0	63·0	63·0
Shoulder	35·7	48·0	3·6	8·0	7·4	4·1
Ankle	32·1	34·6	11·0	5·3	11·1	0
Wrist	10·7	28·0				
Hand	32·1	41·3	3·6	6·7	7·4	5·6
Spine	14·3	49·3	0	16·0	0	12·0
Hip	10·7	32·0	0	12·0	7·4	8·6
Elbow	17·8	24·0	3·6	1·3	—	—
MTP	17·8	20·0	7·1	1·3	—	—
Polyarticular	50·0	72·0	—	—	—	—

ACUTE ARTHRITIS

It is difficult to define acute arthritis. Thirty-four patients described short-lasting episodes of increased pain, lasting only a few hours and resolving spontaneously; these attacks were not analysed further.

We have defined acute attacks as episodes of severe joint pain, usually with swelling, lasting between 12 hours and 4 weeks. By this definition 15 men (54%) and 21 women (28%) had attacks of acute arthritis. They were common in both sexes below 60 years, and relatively more frequent in men at all ages (Table 2). The men also had more attacks than the women: 11 of the 15 men reported more than 3 attacks compared to only 8 of the 21 women.

The knee joint was the most commonly involved site, followed by the wrist, ankle, and hand. Upper

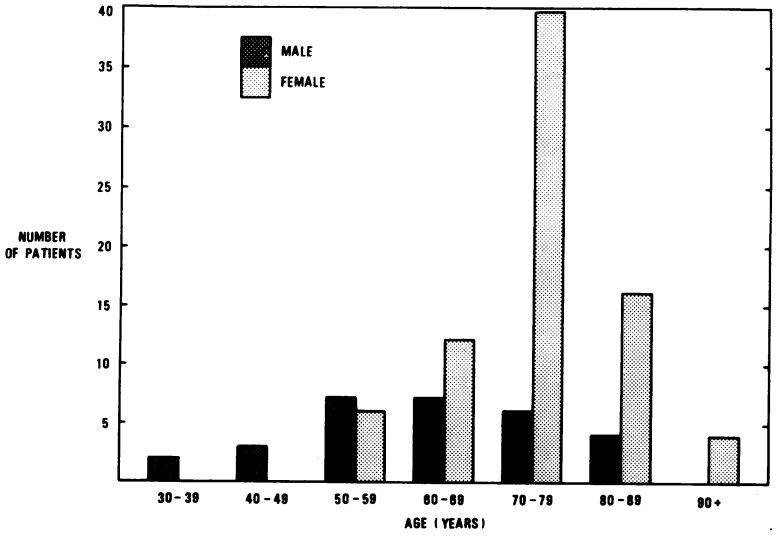

Fig. 1 *Distribution of patients by age and sex.*

Table 2 *Age and sex pattern and distribution of acute attacks in patients with pyrophosphate arthropathy (data available on 103 patients only)*

	Men		*Women*	
	No.	*(%)*	*No.*	*(%)*
Total number	28		75	
Number sustaining acute attacks:	15	(54)	21	(28)
Number sustaining acute attacks:				
Under 60 years	8/12	(67)	2/5	(40)
Over 60 years	7/16	(44)	19/70	(27)
In those sustaining acute attacks: the incidence of recurrent attacks:				
Under 60 years	7/8	(87·5)	2/5	(40)
Over 60 years	4/7	(57·1)	8/19	(42·1)
Distribution:				
Knee		(93)		(71)
Wrist/hand		(13)		(62)
Ankle		(25)		(4·8)
Polyarticular (3 simultaneously)		(13)		(24)

limb attacks were relatively more common in women and the lower limb in men. Polyarticular attacks (3 or more joints involved concurrently) were commoner in women (Table 2).

A total of 13 patients (11 men and 2 women) complained of acute attacks only and had no other joint symptoms.

CHRONIC JOINT DISEASE

The remaining 92 patients had chronic joint disease with or without additional acute episodes.

Table 1 shows the overall distribution of joint involvement. Only 8% of patients did not have knee disease; the majority had polyarticular involvement, the knee being the most severely affected site. The women had a wider spectrum of involved joints, and those with the longest history of arthritis also usually had clinical and radiological evidence of osteoarthritis in the hips, back, and hands.

Of those patients with knee involvement 89% had clinical evidence of an effusion and 85% joint crepitus at the time of the survey. The knees of 30 patients (28 women and 2 men) were severely affected with gross deformity or instability; these changes were bilateral in 11 women.

Hand disease was seen in 76 patients. The distal interphalangeal joint was most often affected, and typical Heberden's nodes were common. The pattern of hand distribution varied (Table 3), increasing with age and being commoner in women than in men. 32% of patients had involvement of the carpometacarpal joint of the thumb and of the metacarpophalangeal and interphalangeal joints of the index and middle fingers (Table 3).

ASSOCIATED JOINT DISEASES (Table 4)

Rheumatoid arthritis. Eight patients had classical or definite rheumatoid arthritis by ARA criteria.[10] Seven were strongly seropositive, 4 had rheumatoid nodules, and one previous rheumatoid vasculitis. Six of these patients had been on chronic steroid therapy (see below).

Table 3 *Distribution of hand disease in patients with pyrophosphate arthropathy (all figures expressed as a percentage)*

Joint involved	*Patient groups divided by age and sex*				
	Men 70 yr (12)	*Women 70 yr (16)*	*Men 70 yr (18)*	*Women 70 yr (57)*	*Overall (103)*
1st CMC	8·3	43·7	22·2	75·4	53·4
MCP	8·3	31·2	33·6	56·1	42·7
PIP	16·7	31·2	55·5	68·4	54·4
DIP	8·3	56·2	83·3	87·9	72·8
CMC+MCP+PIP+DIP	0	25·0	16·7	45·6	32·0

CMC = carpometacarpal joint of the thumb. MCP = metacarpophalangeal joint. PIP = proximal interphalangeal joint. DIP = distal interphalangeal joint.

Generalised OA. A clinical pattern of disease consistent with 'generalised osteoarthritis' was seen in 45 patients. This was common in the women, who often had a long history of joint disease. In 4 cases old radiographs were available and showed evidence of osteoarthritis before the chondrocalcinosis became visible.

Hypermobility. Eight patients had a modified Beigton score of more than 3 at the time of survey; a further 5 patients had a history compatible with previous generalised hypermobility.

Previous knee surgery. Eight patients had a history of knee surgery many years prior to the onset of their presenting complaint. In 3 of these, symptoms and chondrocalcinosis were confined to the operated knee.

Previous steroid therapy. Sixteen patients had been treated with steroids in a dose equivalent to 7·5 mg of prednisolone or more for a minimum of 5 consecutive years. Fourteen of these patients had been given steroids for their joint disease, 6 for rheumatoid arthritis and 8 for presumed polymyalgia rheumatica, one of whom had proved giant cell arteritis. The 6 patients treated for rheumatoid disease had a mean age of 56·5 years, compared with 73 years for those

Table 4 *Incidence of pre- or coexisting joint damage in 105 patients with pyrophosphate arthropathy*

Diagnosis	*28 men*		*75 women*	
	No.	*(%)*	*No.*	*(%)*
Generalised osteoarthritis	5	17·8	40	53·3
Rheumatoid arthritis	2	7·1	6	13·3
Hypermobility	2	7·1	11	14·7
Chronic steroid therapy	2	7·1	14	18·7
Knee surgery (prior to arthritis)	5	17·8	3	6·6
Gout	2	7·1	0	0
None of the above	12	42·8	20	26·7

with girdle pain and stiffness (presumed polymyalgia rheumatica).

Gout. Four patients had previously been diagnosed as having gout. This was confirmed by finding monosodium urate monohydrate crystals in addition to pyrophosphate deposition in two.

There were no significant clinical differences between patients with these associated conditions and those without, except that the 8 rheumatoids were younger than the group as a whole, and only 3 of those on chronic steroid therapy had acute episodes.

RADIOLOGICAL FINDINGS

The overall radiological changes were as previously described[11 12] and present in all patients to varying degrees. Articular calcification was seen as linear and punctate calcification of hyaline and fibrocartilage. These changes were usually bilateral and present in all except 4 patients, who none the less exhibited other typical features of the arthropathy. Fibrocartilage was most densely calcified in the knee menisci, triangular ligament of the wrists, and pubic symphysis; the glenoid and acetabular labia and intervertebral discs were less often involved. Capsular calcification was also noted in the metacarpophalangeal joints, metatarsophalangeal joints, shoulders, and hips; and some periarticular soft tissue calcification occurred in tendons (Achilles, quadriceps, triceps, and supraspinatus).

Typical degenerative changes were seen in nearly all patients. Features included narrowing of the joint space, subchondral sclerosis, cysts, and exuberant osteophyte formation. The knees, wrists, and metacarpophalangeal joints were most often involved, with particularly striking damage in the patellofemoral and radiocarpal joints. The elbow and glenohumeral joints were also frequently affected.

Rapidly progressive destructive changes, with bony collapse and fragmentation of subchondral bone, was seen in 16 patients and resembled Charcot joints. These changes resulted in 7 total hip replacements (6 patients) and 4 knee prostheses (4 patients), and 5 had severely affected shoulders and elbows.

No differences were found in the radiological signs in the different clinical groups except for those with rheumatoid arthritis and the 12 younger men (below 60 years). In the 8 patients with rheumatoid disease by ARA criteria the radiological features were more in keeping with pyrophosphate arthropathy than with rheumatoid arthritis. Only one had the typical soft tissue swelling, juxta-articular osteoporosis and erosions at metacarpophalangeal joints. Two further patients had occasional rheumatoid erosions, but in the remaining 5 a radiological diagnosis of rheumatoid arthritis could not be made.

In the 12 young men radiological evidence of joint damage was minimal. All had chondrocalcinosis of knee menisci, with other joints affected rarely. None had the prominent osteophytes, subchondral sclerosis, or degenerative changes seen in all other patients.

Discussion

Calcium pyrophosphate dihydrate (CPD) is preferentially deposited in fibrocartilage, particularly in the elderly,[13] resulting in characteristic radiological changes, including chondrocalcinosis. All except 4 of our patients had the typical *x*-ray features. Synovial fluid and tissue samples were obtained only when clinically indicated, but in all specimens crystals of calcium pyrophosphate dihydrate were seen.[7] There were no important clinical or radiological differences between those patients in whom pyrophosphate deposition was confirmed microscopically and those with radiological criteria alone, and therefore it is reasonable to equate chondrocalcinosis with CPD in this series.

Pyrophosphate deposition may be asymptomatic.[2 3] This survey differs from previous reported series in including only patients with symptoms of joint disease. Furthermore, patients with evidence of pyrophosphate deposition and a subsequent diagnosis of another rheumatic disease were also included, allowing us to study the whole clinical spectrum associated with CPD. This approach contrasts with other authors, who have often excluded patients with other diagnostic labels, and described the arthropathy according to the classification introduced by McCarty.[14]

The most striking finding in this series was the difference in the disease between men and women. The men were 10 years younger, had a shorter history of disease, and suffered from recurrent acute episodes in the lower limbs. By contrast most of the women had chronic polyarticular disease. Atkins *et al.*[15] suggested a similar age/sex distribution but made no comment on any differences in the pattern of disease. McCarty[2 14] had found acute attacks to be commoner in men, but quoted an equal sex incidence overall. Our findings suggest a marked sex difference in the pattern of disease in unselected patients. The failure of other series to demonstrate this may be due to small numbers or to selection of patients.

McCarty[14] described 'petit attacks' in both gout and pyrophosphate arthropathy. These were common in our patients and characterised by severe pain lasting 2 or 3 hours, with no swelling and resolving spontaneously. The cause of these minor exacerbations was not apparent. The more prolonged acute attacks were generally associated with effusions and were typical of 'pseudogout'.[16] As in previous series, these attacks were commonest in the knees, and 13

patients (11%) had this as their only rheumatological complaint. The men had more pseudogout than the women, though upper limb problems and polyarticular attacks were relatively more frequent in women. Two patients had pseudogout of the first metatarsophalangeal joint ('pseudopodogra').[17] Many of the patients had acute attacks while in hospital for other reasons, as previously described by O'Duffy.[18]

The majority of our patients had a polyarticular chronic arthritis, the knee being the worst affected joint. Large joint involvement was often widespread, many patients having significant problems in shoulders, elbows, and ankles, which are sites not often affected in uncomplicated osteoarthritis.[19] Severe destructive changes were common in the knees, especially in women. Gross instability and angulation deformities were seen, and many patients were unable to walk. The radiological findings included bony collapse and fragmentation of bone, and were similar to the severe destructive changes described by Richards and Hamilton,[20] Menkes *et al.*,[21] and others.

The pattern of small-joint involvement was suggestive of typical generalised osteoarthritis.[19] In addition to Heberden's nodes and first carpometacarpal joint disease, metacarpophalangeal and interphalangeal changes were seen, a distribution and frequency similar to that found in a group of osteoarthritic patients studied in a similar way.[19]

By conventional clinical and radiographic criteria many of our patients could therefore be diagnosed as having osteoarthritis, although they clearly had pyrophosphate deposition as well. The incidence of acute attacks was no different in these patients than in the whole group, and many of those with destructive changes in the knee also had coexisting 'nodal' osteoarthritis. There was both clinical and radiological evidence of a progression from osteoarthritis to a more widespread disease associated with pseudogout or destructive disease in some patients. These findings do not fit easily with the classification suggested by McCarty.[14] In particular, the pseudogout, pseudo-osteoarthritis, and pseudoneurotrophic groups could not easily be distinguished owing to the considerable overlap described above.

In McCarty's classification several of our patients might be diagnosed as having 'pseudorheumatoid arthritis'. However, 8 patients fulfilled ARA criteria for rheumatoid disease[10]; they had a long history, typical joint deformities, nodules or vasculitis (5), and were strongly seropositive (7). The diagnosis of pyrophosphate deposition was relatively recent, and 6 had received chronic steroid therapy. Radiographically it was possible to reach a diagnosis of possible rheumatoid disease in only 3, whereas all 8 had typical CPD.

However, we feel that there can be no doubt that these patients had rheumatoid arthritis. It is possible that the pyrophosphate deposition appeared secondarily, perhaps partly owing to steroid therapy and pre-existing joint damage, and then modified the disease. The mechanisms may be similar to the radiological modification of RA that occurs in association with idiopathic skeletal hyperostosis.[22]

The coexistence of both rheumatoid arthritis and osteoarthritis with pyrophosphate deposition suggests that joint damage from a variety of causes could predispose to chondrocalinosis. Further support for this hypothesis comes from patients with hypermobility and previous joint surgery. The association between osteoarthritis, pyrophosphate arthropathy, and hypermobility has been described by Bird and his colleagues.[23] There are 2 possible explanations: one is that a generalised collagen defect predisposes to both conditions; alternatively, instability could produce local mechanical damage and secondary crystal deposition (perhaps the mechanism in neuropathic joint damage).[24] We have seen several patients in whom chondrocalcinosis is present only in unstable or previously damaged joints,[25] and in the present series 3 patients had deposits only in previously operated knee joints. Although deposition is widespread in some patients with hypermobility, the findings indicate local damage predisposing to crystal deposition in many cases.

Chronic steroid therapy may also predispose to crystal deposition. Steroids damage cartilage and bone,[26] and 16 of our 105 patients had been on long-term treatment. Interestingly, 14 of these 16 had been given steroids for joint disease—for rheumatoid arthritis in 6 cases and for presumed polymyalgia rheumatica in 8. Although the coexistence of polymyalgia and chondrocalcinosis could be the chance association of 2 common phenomena in the elderly, the relatively high incidence in this survey does suggest either that the arthropathy can present with polymyalgic symptoms or that the prescribed steroids predispose to the chondrocalcinosis.

69% of our patients had a pre-existing disease or therapy known to damage articular cartilage. Previous work has assumed that the chondrocalcinosis is a primary event that may then cause several different types of arthritis. However, our clinical and radiological findings are more compatible with crystal deposition occurring as a result of the pre-existing joint damage. Once the crystal deposition has occurred, it must influence the outcome, as severe destructive changes were very common, and the radiological features of RA were obscured.

The hypothesis that emerges from this survey is outlined in Fig. 2. Although several metabolic and other factors may predispose to chondrocalcinosis,

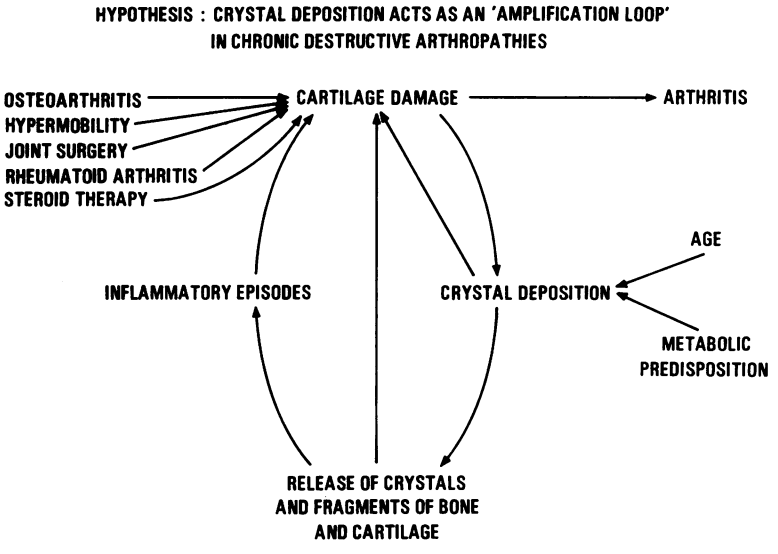

Fig. 2 *Some hypothetical pathways to explain the clinical findings described in the text. It is suggested that pre-existing joint damage predisposes to crystal deposition. The mineral deposits may then accelerate joint damage by mechanical or inflammatory pathways.*

pre-existing cartilage damage may have a major role to play. Crystal deposits may then cause further mechanical and inflammatory damage to a joint, setting up a vicious cycle of disease: an 'amplification loop' in the pathogenesis of chronic arthritis.

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