

A reappraisal of 'analgesic hip'

MICHAEL DOHERTY,¹ MARY HOLT,² PHILIP MacMILLAN,³
IAIN WATT,³ AND PAUL DIEPPE⁴

From the ¹Rheumatology Unit, University Department of Respiratory Medicine, City Hospital, Nottingham; the ²Department of Rheumatology, University Hospital of Wales, Cardiff; and the University Departments of ³Radiodiagnosis and ⁴Medicine, Bristol Royal Infirmary, Bristol

SUMMARY Nineteen patients with hip radiographs typical of 'analgesic hip' (rapidly destructive, atrophic arthropathy involving both femoral and acetabular components) have been studied. Women predominated (14:5), and all were elderly (mean age 74 years, range 64–83 years). Destructive hip disease was unilateral in all but one case. The mean interval from symptom onset to typical *x* ray appearance was short (one year, range three to 24 months), and persistent pain unresponsive to drug therapy was characteristic. Screening showed no metabolic or neurological disease. Contrary to previous reports, non-steroidal anti-inflammatory drugs could not be incriminated in development of the disease. Clinical and radiographic similarity to apatite associated destructive arthritis of other large joints was striking, and occurrence of the latter, uncommon condition in five patients (five shoulders, two knees) suggests that both descriptions represent a common articular response at different joint sites.

Key words: apatite associated destructive arthritis, osteoarthritis, coxarthrosis, destructive arthropathy, non-steroidal anti-inflammatory drugs, indomethacin hip, drug induced arthropathy.

The use of potent non-steroidal anti-inflammatory drugs (NSAIDs), especially indomethacin, has been causally associated with a severe, rapidly destructive arthropathy involving both femoral and acetabular components of the hip. This is characterised radiographically by severe bone attrition, paucity of osteophytes, frequent protrusio acetabuli, and disproportionate retention of joint space—so called 'analgesic' or 'indomethacin hip'.^{1–6} Suggested pathogenic mechanisms include drug toxicity^{7–9} and repeated mechanical insult to a compromised joint rendered less painful by NSAID treatment ('iatrogenic Charcot's arthropathy'^{2–5}). Many of the reported cases, however, have had other risk factors, such as rheumatoid arthritis or steroid therapy, which are implicated in acceleration of joint disease,^{3 4 10–12} and although reported in patients taking NSAIDs for apparently uncomplicated osteoarthritis (OA),^{3–6} the condition is also

described in OA subjects who have not received NSAID medication.³

To further understand the nature of this arthropathy 19 non-rheumatoid patients with characteristic radiographic changes of 'analgesic hip' have been studied in an attempt to define common aetiological factors.

Patients and methods

Nineteen non-rheumatoid patients referred for consideration of hip surgery were selected for study on the basis of characteristic changes on hip *x* ray. Radiographic criteria for selection included: destructive arthropathy showing marked bone attrition and deformity of contour, involvement of both the femoral and acetabular components, disproportionate retention/widening of apparent joint space ± paucity of osteophytes, and protrusio acetabuli. Patients with current or previous films showing predominant focal segmental involvement consistent with avascular necrosis were not included.

A full history was taken and clinical examination, including a full neurological screen, performed on

Accepted for publication 11 September 1985.

Correspondence to Dr Michael Doherty, Consultant Senior Lecturer, Rheumatology Unit, City Hospital, Hucknall Road, Nottingham NG5 1PB.

each patient. Confirmation of drug history was obtained from the patient's general practitioner. Large joints showing effusion were aspirated and the characteristics of the fluid recorded (viscosity, cell count). All joint fluids were examined by polarised light microscopy for presence of birefringent crystals and stained with alizarin red using the technique described by Paul *et al*¹³ for detection of apatite aggregates. Plain radiographs were taken of hands (to include wrists), pelvis, shoulders, knees, thoracolumbar spine, feet, and other clinically involved joints, and examined for evidence of arthropathy and chondrocalcinosis. Laboratory investigations included full blood count, plasma viscosity, urea, urate, ferritin, calcium, phosphate, alkaline phosphatase, thyroxine, free thyroxine index, magnesium, rheumatoid and antinuclear factors, and serological tests for treponemal infection.

Results

Details of the patients are shown in Table 1. There were 14 women and five men with a mean age of 74.3 years (range 64–83 years). Destructive hip disease was unilateral in all but one case. The mean interval between symptom onset and typical radiographic change was short (12 months, range three to

24 months): in five cases previous hip x rays taken near the onset of symptoms were available, showing rapid progression from mild/moderate OA to severe destruction in only three to 18 months. Onset of symptoms was usually rapid and progressive over one to four months: two patients described abrupt onset on a specified day. Severe pain on usage, responding poorly to NSAIDs or analgesics, was characteristic, but night or rest pain were not prominent features. Typical x ray changes are illustrated in Figs 1 and 2.

Ten patients had received NSAIDs (six indomethacin) at conventional dosage for periods ranging from one to 24 months (mean 11 months): four of these had also taken analgesics (Distalgesic or paracetamol) during the same period. Five patients had taken analgesics alone (Distalgesic or paracetamol) for a period of four to 12 months (mean eight months). Four patients had received neither NSAIDs nor analgesics for reasons that included previous peptic ulceration, heart failure, or aversion to medication. No patient had received steroids.

Contralateral hip OA, predominantly of a central pattern, was present in eight patients. 50% of the women had clinical and radiographic evidence of primary nodal generalised OA, and five women (three with nodal OA) had pyrophosphate arthro-

Table 1 Details of patients with destructive hip arthropathy

Sex	Age (years)	Affected hip	Symptom onset to x ray change (months)	Drug therapy		Additional arthropathy				
				Drug	Duration (months)	Contralateral hip OA	Nodal OA	CPPD* deposition	Apatite associated destructive arthritis	Other
F	64	R	18	A*	4	Concentric	+	Knees		
F	69	L	10							
F	71	L	6	A	6	Sup. pole		Knee		
F	71	R	4	A. NSAID	12	Central				
F	72	L	6			Central				
F	72	R	3	NSAID	12	Central	+			
F	73	L	8	A	8		+			
F	76	R	18			Central				
F	78	R	12	NSAID	12		+			
F	78	R	3	A. NSAID	3		+	Knees, wrists, shoulder		
F	80	L	10	NSAID	1		+			
F	81	L	18	NSAID	24		+	Knee, wrists	Shoulder	
F	82	R, L	24	NSAID	24				Shoulders	
F	83	L	12	NSAID				Knees, wrists	Shoulders	
M	65	L	24	A. NSAID	3				Knee	
M	70	R	12			Central				
M	73	L	18	A	12				Knee	
M	75	L	12	A. NSAID	8					AS*
M	78	L	18	A	12	Sup. pole				

*A=analgesic; CPPD=calcium pyrophosphate dihydrate; AS=ankylosing spondylitis.

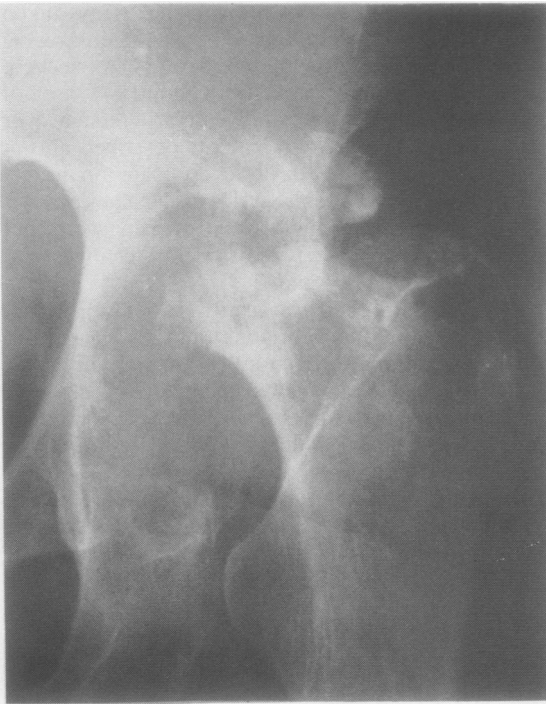


Fig. 1 Hip radiograph of a 73 year old woman with an eight month history of pain, showing severe involvement of both femoral and acetabular components with deformity, bone attrition, lack of osteophyte, and apparent widening of joint space.

pathy \pm chondrocalcinosis affecting knees (five), wrists (three), and shoulders (one) (calcium pyrophosphate dihydrate (CPPD) crystals were identified from at least one joint in all cases).

Five patients (three women, two with CPPD; two men) had similar rapidly destructive disease of other large joints (five shoulders, two knees), with clinical, radiographic, and synovial fluid findings consistent with 'apatite associated destructive arthritis'.¹⁴ Fluids from these joints showed normal viscosity, cell counts of $0.7-10 \times 10^9/l$ (predominance of mononuclear cells), and plentiful alizarin red staining particles appearing as ovoid bodies of $0.5-5 \mu m$ diameter. One patient had clinical and radiographic features of classical ankylosing spondylitis. No patients showed clinical evidence of neurological or endocrine disease. Two patients were brother and sister.

Laboratory screening showed raised plasma viscosity in six patients, anaemia (normal indices) in four, and modest elevation of urea in four: two patients were weakly seropositive for rheumatoid factor. Other tests were normal.

Histological examination of involved hip tissue removed at surgery (four cases) showed similar non-specific changes of cartilage loss, mild synovial cell hyperplasia, and plentiful alizarin red staining particulate matter in synovium with little or no associated inflammatory cell infiltrate. Analytical electron microscopy, performed in two cases, showed intrasynovial particles with morphology and a calcium/phosphorus ratio consistent with apatite. CPPD crystals were not identified in any specimen, and culture of tissue was negative.

Discussion

The clinical and radiographic features of destructive hip disease in these patients appear sufficiently distinctive to warrant consideration as a separate subset of 'joint failure'. Patients were predominantly female and elderly and presented a surprisingly short history of severe pain on usage, with rapid progression to joint destruction. The radiographic appearance of severe bone attrition diffusely affecting both femoral and acetabular components in the absence of reparative changes ('analgesic hip') is striking and was the means of patient selection in this study.

The differential diagnosis of rapidly destructive hip disease includes atrophic Charcot's arthropathy, avascular necrosis, sepsis, pyrophosphate arthropathy, and advanced OA. Despite striking radiographic similarity to atrophic Charcot joints, none of the patients in this study had evidence of neurological damage or of disease predisposing to Charcot's arthropathy. Two of the patients described sudden onset of pain, but the x ray changes diffusely involved both sides of the joint space as opposed to single bone involvement seen in avascular necrosis. Osteopenia and erosive change were not radiographic features, and no infective cause was found on tissue examination. The radiographic appearance is unlike that of chronic pyrophosphate arthropathy, which usually is associated with hypertrophic changes, cyst formation, and joint space narrowing;¹⁵ furthermore, no patient had radiographic hip chondrocalcinosis. The clinical and radiographic features were also incompatible with simple OA in view of the lack of osteophyte and cyst formation, disproportionate retention of apparent joint space, diffuse attrition of bone, and rapid progression.

Previous reports of similar, rapidly destructive hip disease have emphasised the possible role of NSAIDs in the pathogenesis of the condition.^{1-6 9 12} Support for this putative association has come firstly from in vitro demonstration that NSAIDs, especially indomethacin, inhibit sulphated glycosa-

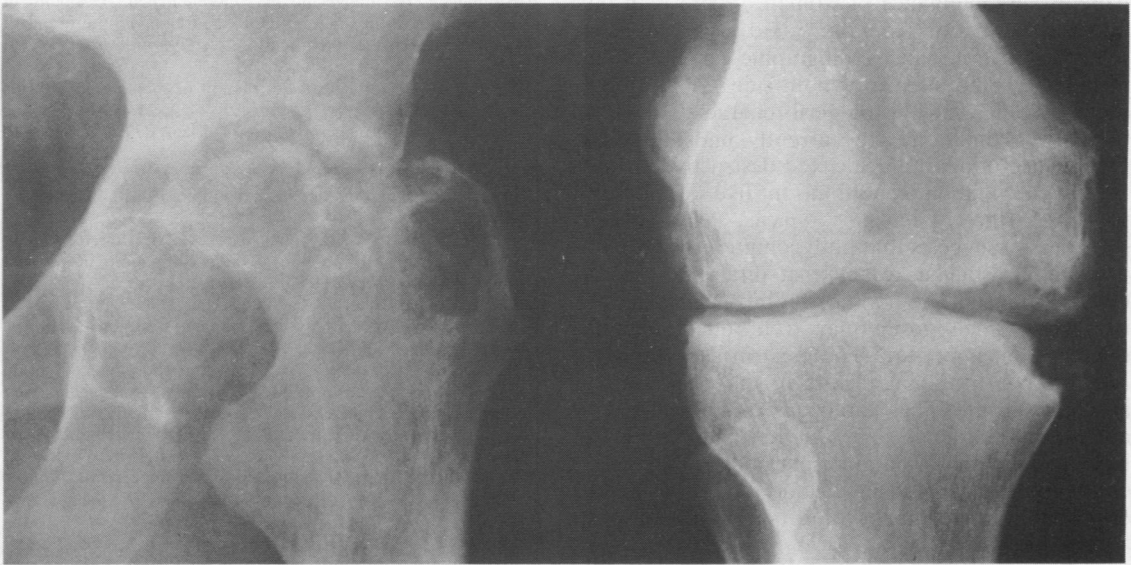


Fig. 2 Hip and knee radiographs of a 65 year old man. (Symptoms at both sites predated x ray changes by 24 and three months respectively.) The hip shows severe destructive disease involving both sides of the joint, with deformity, paucity of osteophyte, protrusio, and apparent widening of joint space. The knee radiograph shows unicompartmental destructive disease involving both femoral and tibial components, with bone attrition, deformity, and lack of osteophyte. Clinically the knee was unstable with a large cool effusion: synovial fluid findings included normal viscosity, moderately raised cell count, and numerous alizarin red staining calcific particles.

minoglycan synthesis in aged human cartilage,⁷ reduce fracture healing in rats,¹⁶ and inhibit bone remodelling in rabbit and rat models;^{17 18} and, secondly, from a retrospective radiographic survey of patients with hip OA, which reported more rapid progression and joint destruction in patients who had received indomethacin compared with those who had been on other NSAIDs, analgesics, or no medication.⁹ Watson, however, in a prospective study of patients with hip OA¹⁹ found no correlation between femoral head height loss and NSAID intake, implicating instead obesity as a major determinant of destructive change. In the present study only 10 of 19 patients had received NSAIDs and four had been on no medication at all. Although a contributory effect of NSAIDs in those taking the drugs cannot be excluded, it is at least apparent that this rapidly destructive arthropathy can occur as an independent event unrelated to medication and does not reflect a specific effect of NSAID usage. The prominence of pain in our patients, even in those persisting with NSAID therapy, would seem to discount 'overuse' of a compromised joint rendered insensible by drugs or disease as a plausible mechanism to explain this condition.²⁻⁵

Although the patients in this study represent a small and uncontrolled group, it is of interest that

50% of women had generalised nodal OA and that five patients had pyrophosphate arthropathy at other sites. Destructive joint disease simulating neuropathic arthropathy has previously been described in patients with CPPD deposition.^{20 21} In none of the present cases, however, was there radiographic or histological evidence to implicate local CPPD deposition in the pathogenesis of rapid hip destruction. The possibility, however, that OA or pyrophosphate arthropathy at distant sites may be associated with a different disease at the hip is intriguing. Gerster *et al*²² have documented a greater frequency of destructive arthritis (at sites including the hip) in patients with generalised OA alone, and Menkes *et al*²³ have reported a similar association of an increased frequency of chondrocalcinosis at other sites in patients with destructive hip disease unrelated to crystal deposition. Mechanisms to link directly a chronic, hypertrophic arthropathy (pyrophosphate arthropathy) to a markedly atrophic, rapidly destructive arthropathy of the hip remain speculative, and confirmation of the association is awaited.

Similarity between the hip disease described in our patients and apatite associated destructive arthritis of other joints¹⁴ is striking. Both conditions are characterised by large joint disease in elderly

patients, predominance of women, severe pain on usage as the major symptom, rapid progression to joint destruction, and radiographic changes that include atrophic disease of both sides of the joint (Scintigraphic and histological characteristics of these two conditions are currently under study.) Occurrence of apatite associated destructive arthritis, an uncommon condition, in five of our 19 patients (three having typical 'Milwaukee' shoulders²⁴) suggests that both conditions represent a common articular response at different sites in elderly subjects. The finding of a brother and sister in such a small group may well reflect patient selection but is of further interest in supporting a role for constitutional factors in the response to articular insult. The pathogenic significance of apatite in destructive joint disease, and the possibility that the condition represents a distinct disease entity or the occasional outcome of various joint disorders, however, have yet to be established.^{14 25}

We would like to thank the Arthritis and Rheumatism Council for financial support.

References

- 1 Coke H. Long term indomethacin therapy for coxarthrosis. *Ann Rheum Dis* 1967; **26**: 346-7.
- 2 Arora J S, Maudsley R H. Indocid arthropathy of hips. *Proc R Soc Med* 1968; **61**: 669.
- 3 Allen E H, Murray O. Iatrogenic arthropathies. *European Association of Radiology, Proceedings Excerpta Medica (International Congress Series)* 1971; **249**: 204-10.
- 4 Milner J C. Osteoarthritis of the hip and indomethacin. *J Bone Joint Surg* 1973; **54B**: 752.
- 5 Solomon L. Drug-induced arthropathy and necrosis of the femoral head. *J Bone Joint Surg* 1973; **55B**: 246-61.
- 6 Hauge M F. Hoftleddsartrose-indometacin. *Tidsskr Nor Laegeforen* 1975; **95**: 1594-6.
- 7 McKenzie L S, Horsburgh B A, Ghosh P, Taylor T K F. Effect of anti-inflammatory drugs on sulphated glycosaminoglycan synthesis in aged human articular cartilage. *Ann Rheum Dis* 1976; **35**: 487-97.
- 8 Watson M. The suppressing effect of indomethacin on articular cartilage. *Rheumatol Rehabil* 1976; **15**: 26-30.
- 9 Rønningen H, Langeland N. Indomethacin treatment in osteoarthritis of the hip joint. Does the treatment interfere with the natural course of the disease? *Acta Orthop Scand* 1979; **50**: 169-74.
- 10 Isdale I C. Femoral head destruction in rheumatoid arthritis and osteoarthritis. *Ann Rheum Dis* 1962; **21**: 23-30.
- 11 Storey G O. Bone necrosis in joint disease. *Proc R Soc Med* 1968; **61**: 961-9.
- 12 Bossingham D H, Schorn D, Morgan G W, Mowat A G. Progression of hip disease in rheumatoid arthritis. *Rheumatol Rehabil* 1978; **17**: 170-8.
- 13 Paul H, Reginato A J, Schumacher H R. Alizarin reds staining as a screening test to detect calcium compounds in synovial fluid. *Arthritis Rheum* 1983; **26**: 191-200.
- 14 Dieppe P A, Doherty M, MacFarlane D G, Hutton C W, Bradfield J W, Watt I. Apatite-associated destructive arthritis. *Br J Rheumatol* 1984; **23**: 84-91.
- 15 Resnick D, Niwayama G. Calcium pyrophosphate dihydrate (CPPD) crystal deposition disease. In: *Diagnosis of bone and joint disorders*. Philadelphia: Saunders, 1981; **2**: 1520-74.
- 16 Rø J, Sudmann E, Marton P F. Effect of indomethacin on fracture healing in rats. *Acta Orthop Scand* 1976; **47**: 588-99.
- 17 Sudmann E. Effect of indomethacin on bone remodelling in rabbit ear chambers. *Acta Orthop Scand* 1975; (suppl 160): 91-115.
- 18 Huusko P J, Nieminen L H E, Nieminen L S. The effect of indomethacin on tooth extraction wound healing in rats. *Experientia* 1975; **3**: 1056-8.
- 19 Watson M. Femoral head height loss: a study of the relative significance of some of its determinants in hip degeneration. *Rheumatol Rehabil* 1976; **15**: 264-9.
- 20 Richards A J, Hamilton E B D. Destructive arthropathy in chondrocalcinosis articularis. *Ann Rheum Dis* 1974; **33**: 196-203.
- 21 Menkes C J, Simon F, Delrieu F, Forest M, Delbase F. Destructive arthropathy in chondrocalcinosis articularis. *Arthritis Rheum* 1976; **19** (suppl 3): 329-48.
- 22 Gerster J C, Vischer T L, Fallet G H. Destructive arthropathy in generalised osteoarthritis with articular chondrocalcinosis. *J Rheumatol* 1975; **2**: 265-9.
- 23 Menkes C J, Decraemere W, Postel M, Forest M. Chondrocalcinosis and rapid destruction of the hip. *J Rheumatol* 1985; **12**: 130-3.
- 24 McCarty D J, Halverson P B, Carrera G F, Brewer B J, Kozin F. 'Milwaukee shoulder'—association of microspheroids containing hydroxyapatite crystals, active collagenase, and neutral protease with rotator cuff defects. I Clinical aspects. *Arthritis Rheum* 1981; **24**: 464-73.
- 25 Nuki G. Apatite associated arthritis. *Br J Rheumatol* 1984; **23**: 81-3.