The arthropathy of cystic fibrosis

JOSH DIXEY,¹ ANDREW N REDINGTON,² ROBIN C BUTLER,¹
MICHAEL J SMITH,² JOHN R BATCHELOR,³ DAVID F WOODROW,¹
MARGARET E HODSON,² JOHN C BATTEN,²
AND DERRICK A BREWERTON¹

From ¹*Charing Cross and Westminster Medical School;* ²*Brompton Hospital;* and the ³*Royal Postgraduate Medical School, London*

SUMMARY Musculoskeletal symptoms are frequent in cystic fibrosis (CF). Here the clinical features of 29 patients with CF who had significant arthropathy are described. Twelve had episodic arthritis (EA) characterised by repeated short attacks of severe, incapacitating polyarthritides, which in seven was associated with fever and erythema nodosum. Ten patients had hypertrophic pulmonary osteoarthropathy (HPOA). The onset of symptoms in the group with HPOA was usually later (mean age 20 years v 16 years for EA) and was associated with significantly worse lung function than in patients with CF, either without arthropathy or with EA. Seven patients had arthropathies which could not be classified as EA or HPOA.

Key words: episodic arthritis. pulmonary osteoarthropathy.

In recent years the life expectancy of patients with cystic fibrosis (CF) has improved,^{1,2} and many patients survive to adult life. As a consequence, rheumatic disorders are now commonly observed in older patients. Two distinct arthropathies have been described in CF: episodic arthritis (EA), which appears to be more common in children^{3,4} but has been reported in adults⁵; and hypertrophic pulmonary osteoarthropathy (HPOA), which is normally confined to adults⁵ but has been described in children.^{6,7} Both EA and HPOA have been the subjects of reports of individual cases.^{8–13} So far, there have been no prospective studies of these arthropathies in patients with CF. To define the clinical and pathological characteristics in more detail and to prepare for a continuing research programme we studied all patients attending our clinic who complained of musculoskeletal symptoms.

Patients and methods

Approximately 250 patients attend the Brompton Hospital adult cystic fibrosis clinic. Since 1983 all patients with rheumatic symptoms have been referred for rheumatological assessment.

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Correspondence to Professor D A Brewerton, Rheumatology Department, Westminster Hospital, 17 Page Street, London SW1P 2AP.

DIAGNOSIS

Episodic arthritis was diagnosed when there was history of repeated attacks of severe polyarthropathy with clear resolution of symptoms between attacks. HPOA was diagnosed on the basis of the following clinical features: (a) finger clubbing, (b) chronic symmetrical pain or swelling, or both, of the wrist, knee, or ankle, and (c) the presence of periostitis on radiographs or a positive ^{99m}Tc hydroxydiphosphonate (HDP) bone scan, or both. A significant number of patients with rheumatic symptoms did not conform to EA or HPOA, and they are considered separately.

INVESTIGATIONS

Whenever possible the following investigations were performed while the patient was symptomatic: full blood count, erythrocyte sedimentation rate (ESR), biochemical profile including plasma uric acid concentration, RAHA (rheumatoid arthritis haemagglutination test) rheumatoid factor (RF), antinuclear factor (ANF), immunoglobulin concentrations, C3 and C4 complement levels, immune complex (IC) titre (enzyme linked immunosorbent assay (ELISA) Flexia system; Pharmacia (UK) Ltd), and HLA analysis (class I antigens). Radiographs were taken of the affected joints, and in six of the patients with HPOA ^{99m}Tc HDP bone scans were performed. Knee arthroscopy was performed under local

anaesthesia using a Storz paediatric arthroscope in one patient with EA and in one patient with HPOA. The synovial biopsy specimens obtained were fixed for routine light and electron microscopy, and tissue was snap frozen for immune studies. In all patients the forced expiratory volume in one second (FEV₁) and the forced vital capacity (FVC) were recorded on a spirometer and values expressed as percentage predicted for age, height, and sex.¹⁴ Lung function data were expressed as mean (SD). The EA and HPOA groups were compared with each other and with a group of 170 patients with CF without arthropathy (mean age 19 (SD 1.2) years) using the Mann-Whitney U test. Permission for this study was obtained from the Brompton Hospital ethics committee.

Results

CLINICAL FEATURES

Episodic arthritis

Twelve patients had a clinical diagnosis of EA. The age of onset varied considerably (mean 16 years, range 5–29), but attacks usually started in adolescence. In those with an early onset parents reported that there had been complaints of severe widespread joint pains of sudden onset with flu-like symptoms. Frequently, an acute infection was diagnosed and antibiotics were prescribed. In most episodes we have observed, the patients were temporarily unable to walk because of severe lower limb pain. Many looked miserable because of the pain and lay still in bed. Typically, there was erythema over the finger joints, with tenderness over most peripheral joints but little swelling. Although active joint movement was limited, the passive range was usually normal. Attacks lasted an average of four days, and the joints then returned to normal. One of the 12 patients had severe symptoms which persisted for up to two weeks. Seven patients developed a high, swinging fever and a rash which was typical of erythema nodosum, being present on the legs and occasionally also on the forearms. Eight patients continued to have attacks one to three years after diagnosis, and in two patients the attacks have occurred at frequent intervals over a much longer period (11 and 17 years). In a further two, attacks started in childhood and stopped after puberty. Only one patient was not taking pancreatic supplements. This patient stopped his enzyme supplements because he believed that they provoked his attacks of EA. He was unwilling to undergo a provocation test. In most patients non-steroidal anti-inflammatory drugs (NSAIDs) led to rapid symptomatic relief. In one patient, however, attacks of EA were unresponsive to NSAIDs but responded to prednisolone.

Hypertrophic pulmonary osteoarthropathy

Ten patients had HPOA. The age of onset tended to be later than in the patients with EA (mean 20 years, range 15–21 years). The onset was usually insidious, with bone pain in the region of wrists, knees, and ankles. At first, the pain was not severe but progressed steadily to a continuous and troublesome ache with symmetrical swelling and periarticular tenderness of the large joints. In most patients the joint disease had a symmetrical pattern affecting wrists (six), knees (nine), and ankles (seven). Knee effusions were common; in severe disease the patients experienced difficulty in walking because of ankle pain. The small joints of hands and feet were involved in one patient. In three patients there was an exacerbation of joint symptoms during chest infections, and, in one, the size of the knee effusion regularly reflected the severity of the acute exacerbations of his chest disease. All the patients were taking pancreatic supplements. At the onset of HPOA the pain usually responded to NSAID therapy, but drug therapy became less effective as the disease progressed.

Miscellaneous

Seven patients had rheumatic disorders which could not be classified as HPOA or EA. Three had clinical features similar to HPOA but with no periosteal reaction on radiography. One woman had intermittent myalgia induced by exercise, and one man had the clinical features of ankylosing spondylitis. A 16 year old woman had suffered from a chronic painless tenosynovitis over the dorsum of both wrists and ankles for 10 years. A man developed classical seropositive rheumatoid arthritis (RA) at the age of 31 years.

In addition to the 29 patients included in this report, many patients with CF were examined who complained of chronic knee pains. No significant arthropathy could be demonstrated and in most patients the symptoms were mild and not incapacitating. These patients were not investigated further.

PATHOLOGICAL FINDINGS

Episodic arthritis

Rheumatoid factor and ANF were not detected and the plasma urate was normal. Blood was taken during attacks of EA in five patients with the following abnormal findings: a raised white blood cell count (WBC) count in two (12 and $19 \times 10^9/l$); a raised ESR in four (range 12–55 mm/h); a raised IC titre in one (141 IU/l, normal range (NR) <20 IU/l). The immunoglobulin and complement levels were normal in all five patients.

One patient with EA was investigated in more detail during an acute attack. Plasma C reactive

protein was raised to 152 mg/l (NR <10 mg/l). Knee arthroscopy was normal apart from a small quantity of synovial fluid with minimal evidence of inflammation (20 neutrophils/ml, protein 16 g/l). A synovial biopsy specimen showed no abnormality on light microscopy, and immunofluorescent staining was negative apart from a few small deposits of IgM on endothelial cells. On ultrastructural examination there was a conspicuous reduplication of the endothelial basal lamina.

Hypertrophic pulmonary osteoarthropathy

The WBC count was raised in five patients (range $14\text{--}21 \times 10^9/\text{l}$) and the ESR was raised in eight (range 22–95 mm/h). Immune complexes were present in three (63, 92, and 884 IU/l). Rheumatoid factor and ANF were not detected. Serum IgM was normal. Seven patients had raised IgG (range 16.8–23.1 g/l, NR 6.3–16.0 g/l) and IgA (range 3.2–6.9 g/l, NR 0.7–3.2 g/l). Complement C3 levels were all normal, but complement C4 levels were depleted in five patients (range 0.12–0.23 g/l, NR 0.25–0.75 g/l).

Knee arthroscopy was performed in one patient. The synovial membrane was normal in appearance, apart from the presence of a fibrinous exudate. The synovial fluid contained 560 WBCs/ml (95% lymphocytes), protein 32 g/l. On light microscopy there was engorgement of blood vessels with mononuclear infiltrate. Specific immunofluorescent staining showed a prominent coating of IgM on endothelial cells, occasional granules of C3 on vessel walls, and positive staining for fibrinogen on the lining layer.

Ultrastructural examination showed a conspicuous reduplication of capillary basal laminae and focal loss of endothelial cells with partial occlusion of some capillaries by fibrin and platelets (Fig. 1).

HLA TYPING

In both groups of patients there was a normal distribution of class I HLA antigens when compared with normal controls in a Caucasian population and with patients with CF without arthropathy.

DIAGNOSTIC IMAGING

In EA the radiographs taken of the most symptomatic joints (normally hands, wrists, and knees) were invariably normal. A $^{99\text{m}}\text{Tc}$ HDP bone scan, performed in one patient during an acute attack of EA, was normal.

Periostitis at the distal ends of long bones was present in nine patients with HPOA (Fig. 2a). Of the six $^{99\text{m}}\text{Tc}$ HDP bone scans performed, four had 'hot' areas corresponding to the periostitis seen on radiography (Fig. 2b). One patient had a positive bone scan accompanied by normal radiographs and one had a normal scan but a marked periosteal reaction on radiography.

LUNG INVESTIGATIONS

In EA the percentages of predicted normal values for FEV₁ and FVC (mean (SD) 58 (14)% and 70 (25)% respectively) were not significantly different from the values for control patients with CF without arthropathy (Fig. 3). *Pseudomonas aeruginosa* was

Fig. 1 Electron micrograph of part of a capillary wall showing discontinuity in the endothelial cell lining (long arrow) and multiple basal laminae (short arrows) in a patient with CF and HPOA. (Uranyl acetate and lead citrate.)

Fig. 2 (a) Wrist radiograph and (b) bone scan of a patient with CF and HPOA showing periosteal new bone formation at the distal ends of radius and ulna bones (a) and increased uptake of radioisotope indicative of periostitis (b).

Fig. 3 FEV₁ values (percentage predicted for weight, height, and sex) in patients with CF without arthropathy (n=170), CF+HPOA (n=10), and CF+EA (n=12); p values refer to Mann-Whitney U tests. (FEV₁=forced expiratory volume in one second; CF=cystic fibrosis; HPOA=hypertrophic pulmonary osteoarthropathy; EA=episodic arthritis.)

present in the sputum of nine patients, with additional *Staphylococcus aureus* in two. In one patient no pathogens were isolated on repeated sputum culture.

In patients with HPOA the percentage predicted FEV₁ was 26 (5)%, which was significantly worse than for those with EA ($p < 0.05$) (Fig. 3). The FVC percentage predicted was also significantly worse when compared with the group with EA (46 (9)% v 73 (25)%; $p < 0.01$) and with the control group (70 (24)%; $p < 0.001$). All patients with HPOA had positive sputum cultures for *P aeruginosa*.

Discussion

Although arthritis has been little recognised as a complication of cystic fibrosis (CF), it is now established as a major cause of pain and disability in approximately 10% of young adults with this disease, and it is evident that arthritis will become more common as patients live longer. Most patients have one of two types of arthritis: episodic arthritis or hypertrophic pulmonary osteoarthropathy, which can usually be readily distinguished on clinical grounds.

Clinically, EA associated with CF is unique. Repeated attacks of severe, generalised joint pain requiring bed rest, often accompanied by fever and erythema nodosum, and with complete resolution of joint symptoms within four days, cannot be satisfactorily explained by other forms of recurrent arthritis, such as reactive arthritis following genitourinary or gut infections,¹⁵ erythema nodosum,¹⁶ palindromic rheumatoid arthritis,¹⁷ or intestinal bypass arthritis,¹⁸ none of which has the same clinical features. Only familial Mediterranean fever (FMF)¹⁹ is similar in the severity of the arthritis, the pattern of the attacks, and the fever, but our patients with EA lacked the other clinical features, racial characteristics, and family history of FMF, and there is no known association between CF and FMF, either in individuals or in families. A metaraminol provocative test was not indicated.²⁰

In HPOA the clinical onset is insidious and the course is related to the severity of the lung disease. On occasions, exacerbations of the arthritis parallel the worsening of the chest infection.⁴⁻⁹ *P aeruginosa* is the dominant pathogen in the sputum, but it is no more common in patients with HPOA than in EA or in CF without arthritis.

The pathogenesis of both EA and HPOA is obscure. From the limited histological material and the immunological investigations in our study, the evidence of inflammatory and immunological responses is sparse and probably no more than may be expected in the presence of persistent chest infec-

tion. The absence of an association between EA and HLA-B8 is also important because in sarcoidosis both erythema nodosum and acute arthritis are associated with B8.²¹⁻²² The further possibility of a genetic component linked to the CF related gene on chromosome 7²³ has been considered and will be investigated when appropriate techniques are available.

Despite the lack of similarity between EA and HPOA and reactive arthritis following genitourinary or gut infection (including the absence of an association with HLA-B27), further investigation of the role of chest or gut infection is indicated. It is also necessary to exclude the possibility that EA may be an adverse reaction to pancreatic supplements. Finally, because of the evidence that neurogenic mechanisms may be involved in clubbing of the fingers, in periosteal reactions, in HPOA, and in CF,²⁴⁻²⁶ there is now a new indication and a new opportunity to investigate neurogenic mechanisms in both EA and HPOA.

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