Juvenile Ankylosing Spondylitis

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Fifteen patients with juvenile ankylosing spondylitis were reviewed. Eight presented with extraspinal arthritis. Certain clinical features were of value early in the disease in distinguishing these patients from those with juvenile rheumatoid arthritis: male sex, remittent oligoarthritis, late onset in childhood, relative sparing of hands and wrists, infrequent cervical spine involvement, and negative tests for rheumatoid factors and antinuclear antibodies. Roentgenographic demonstration of sacroiliac arthritis with reactive sclerosis makes the diagnosis virtually certain.

Ankylosing spondylitis is usually considered to be a disease which affects young adult males; however, onset may be in adolescence or childhood. Diagnosis is often delayed in these patients, and confusion with juvenile rheumatoid arthritis is common. During the past 10 years, 15 patients with juvenile ankylosing spondylitis have been followed in this clinic. In the present study these cases were reviewed with particular attention to features which may permit early diagnosis and differentiation from juvenile rheumatoid arthritis.

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MATERIALS AND METHODS

Fifteen patients with ankylosing spondylitis with onset prior to the age of 17 years were seen in the period 1960 to 1969. Two hundred and eight patients with juvenile rheumatoid arthritis were observed during the same time. Criteria that were used for the diagnosis of ankylosing spondylitis were modified from those proposed by the Third International Symposium on Population Studies in the Rheumatic Diseases (1). Diagnosis is based upon three features of the disease: a) pain, tenderness or stiffness in the low back, or pain in the buttocks, thighs or hips, or radiating into the legs, b) loss of mobility of the back, and c) radiologic diagnosis of sacroiliac arthritis characteristic of ankylosing spondylitis.

Onset of illness was defined as either pain or stiffness in the spine or objective signs of inflammation in an extraspinal joint. Pain on movement or restricted mobility of the back, tenderness on percussion over the spine or sacroiliac joints, or paravertebral muscle spasm were signs of involvement of the spine. Decreased chest expansion or a positive Schober's test were at times present. Sometimes pelvic compression, straight leg raising, Spurling's test or Patrick's test were confirmatory.

Criteria for the diagnosis of juvenile rheumatoid

arthritis were those that were used in previous studies (2). Functional class was determined according to Steinbrocker *et al* (3).

Patients were recalled for examination who had not been seen within the final 2-year period of the study, and in whom the diagnosis of ankylosing spondylitis was established or suspected. Roentgenograms of affected joints and spine were obtained on all patients. Radiologic views of the spine included: frontal and lateral projections of the dorsal and lumber segments, and frontal stereoscopic views of the sacroiliac joints with 20° craniad angulation of the central beam. A single anteroposterior film of the pelvis was evaluated in 26 patients with juvenile rheumatoid arthritis.

Rheumatoid factors were tested by the latex fixation method of Singer and Plotz (4). Tests for antinuclear antibodies were performed by the indirect fluorescent method with young mouse liver as substrate (5). Serum protein electrophoresis was done on cellulose acetate as supporting medium (6). Serum immunoglobulins were determined by the radial diffusion method of Mancini, Carbonara, and Heremans (7) as modified by Fahey and McKelvey (8). Immunoelectrophoresis of serum proteins was performed according to the method of Scheidegger (9).

RESULTS

There were 13 males and 2 females in the study group (Table 1). Their present age range is 13–44 years with a median of 20 years. Duration of disease is 3–33 years with a median of 10 years.

Onset was remittent and mild in the majority of patients, and fluctuations in disease activity continued for months or occasionally years. In Table 2, their ages of onset are compared with those observed in 200 children with juvenile rheumatoid arthritis.

The distribution of clinically detected articular involvement at onset and during the course of the disease is shown in Table 3. Extraspinal involvement was asymmetric at onset in 6 of the children and remained asymmetric during the course of the disease in 10. Extraspinal arthritis preceded symptoms of spinal involvement by 2–13 years in 8 patients. Seven patients had pain in the lumbar spine or sacroiliac joints as their initial symptom. One boy had simultaneous onset of pain in the sacroiliac joints and cervical spine. Five patients have developed heel pain during the course of their illness.

One patient had a brief episode of fever at onset. No patient had rheumatoid rash, nodules or an onset resembling that seen in the systemic presentation of juvenile rheumatoid arthritis. Sciatica has been a prominent symptom in 2 patients. Typical thoracic pain occurred in only one male. One patient had a myelogram and laminectomy elsewhere for disc disease before the true nature of his back pain was appreciated. Aortitis (10–12) has not developed in any of these patients. None has ulcerative colitis or regional enteritis. Minimal lesions of psoriasis appeared 9 years after onset in one patient. One patient developed acute iritis (13–14) 5 years after peripheral joint disease and before spondylitis was recognized. She has no residual eye damage or reduction in visual acuity in spite of repeated attacks of iritis for 13 years. No evidence of ankylosing spondylitis or rheumatoid arthritis was elicited by history in the first-degree relatives of these patients.

Laboratory Findings

No patient had an hematocrit less than 35% or a white cell count greater than 13,000/cu mm. The Westergren sedimentation rate was increased in 13 patients to 24–101 mm/hr and tended to reflect the degree of clinical activity. Tests for rheumatoid factors and antinuclear antibodies were negative in all patients. One patient had an increase in serum concentration of α-2 globulins to 9.4 mg/ml and of γ globulins to 33.8 mg/ml. In this patient the

Table 1. Clinical Data in 15 Patients with Ankylosing Spondylitis

Sex	Age of onset (yr)	Current age (yr)	Initial area of involvement	Major peripheral joints objectively involved during course of disease (+, one; ++, both)					
				Foot	Ankle	Knee	Hip	Shoulder	Elbow
M	11	18	Left ankle	+	+	+	+		+
M	12	19	Left calcaneus	+	+	++	++		
M	11	31	Right knee	+	+	++			+
M	13	23	Lumbar spine	+	++	+	++		
M	13	24	Lumbar spine	+	+	++	+	+	
M	16	20	Sacroiliac joints + cervical spine					+	+
M	8	13	Sacroiliac joints		++	++	+		
M	13	18	Elbow	+	+	+	+		
F	7	31	Knees			++			
M	8	31	Right knee		++	++	++		
M	8	22	Left ankle		++	++	++		
F	16	35	Lumbar spine			+	++	+	
M	14	36	Lumbar spine						
M	5	15	Knees	++	++	++			
M	11	44	Lumbar spine	+					

serum IgG and IgA were increased to 20.19 and 6.80 mg/ml respectively. Immunoglobulin determinations in the other patients were within the normal range. The serum proteins were qualitatively normal in all patients on immunoelectrophoresis.

Synovial fluid from a knee was examined in 4 patients at onset of disease. These fluids were inflammatory in type (Group II).

Roentgenologic Findings

The demonstration of sacroiliac arthritis is the hallmark of ankylosing spondylitis. In these children the development of the classical appearance of such arthritis was often delayed. The normal roentgenologic appearance is shown in Figure 1. The characteristic abnormalities of the disease are shown for contrast in Figure 2. The initial abnormality in the sacroiliac joints appeared to be asymmetric or unilateral in 4 patients. The relationship between the occurrence of sacroiliac changes and duration of disease dated from presenting symptoms is depicted in Table 4. There was a progressive increase in the number of patients demonstrating fusion of the sacroiliac joints with time, although in 2 patients fusion had not occurred after 24 years of disease. Views of the sacroiliac joints were not available in 7 patients during the first year of the disease.

Table 2. Age of Onset of Patients with Ankylosing Spondylitis Compared to Those with Juvenile Rheumatoid Arthritis

Age of onset (yr)	Number of patients	
	Ankylosing spondylitis	Juvenile rheumatoid arthritis
0–4	0	80
5–9	5	74
10–14	8	43
15–16	2	3

Table 3. Clinical Articular Involvement at Onset and During the Course of the Disease

Joint(s) involved	Number of patients		
	Initial	Subsequent	Bilateral involvement
Spine	7	15	
Sacroiliac and lumbar	7*	15	
Dorsal	0	7	
Cervical	1*	4	
Peripheral	8	14	
Knee	4	13	8
Ankle	2	9	5
Hip	0	9	6
Calcaneus	1	5	1
Elbow	1	3	0
Feet, tarsus	0	3	0
Shoulder	0	2	0
Temporomandibular	0	1	1
Hand, proximal interphalangeal	0	1	0
Wrist	0	0	0

* One patient had simultaneous sacroiliac and cervical spine involvement at onset.

Examination of the sacroiliac joints in a comparative series of 26 patients with juvenile rheumatoid arthritis showed definite sacroiliac involvement in 2 patients. Figure 3 is the roentgenogram of one of these patients. Reactive sclerosis was not present in patients with juvenile rheumatoid arthritis to the degree that was seen in ankylosing spondylitis.

In this study of ankylosing spondylitis, there was a progressive increase with time in the occurrence of roentgenologic abnormalities of the lumbar spine (Table 5). These were often delayed in appearance after onset of symptoms or after the radiologic diagnosis of sacroiliac arthritis. Paravertebral subligamentous calcification was the last sign to develop (Fig 4). Abnormalities of the lumbar spine were absent in one patient 24 years after diagnosis and in another after 33 years. Seven patients eventually manifested abnormalities of the dorsal spine. The cervical spine was involved in 4 patients. The symphysis pubis was involved in 2 patients and marginal irregularity of the ichia was present in 3. Other characteristic roentgenologic abnormalities included calcaneal erosions or spurs in 5 patients and narrowing of the cartilage space of the hip joints in 9 patients. In 3 patients, destructive disease of the hips developed. The frequency of hip disease did not appear to be greater in those children with the earliest onset of disease.

Pathology

Synovial tissue was available from a hip in 3 patients and from an elbow in one at the time of arthroplasty, and from diagnostic biopsy of a knee early in the disease in 4 children. The range of histologic findings of villous hypertrophy, synovial cell hyperplasia, endothelial proliferation and round cell infiltration was indistinguishable from the synovitis that is seen in rheumatoid arthritis (15–16). One patient had a biopsy of a sacroiliac joint because unilateral disease had been misinterpreted as a possible infection.

Prognosis

An estimation of the present functional class of these patients is shown in Table 6. Both patients in Class III have disability primarily related to involvement of the hips. Vitallium cup arthroplasty has been performed in 3 patients. The results in 2 would be classified as good and poor in the remaining one. Relative fixation of the dorsal and lumbar spines has occurred in 7 patients. A satisfactory erect posture has

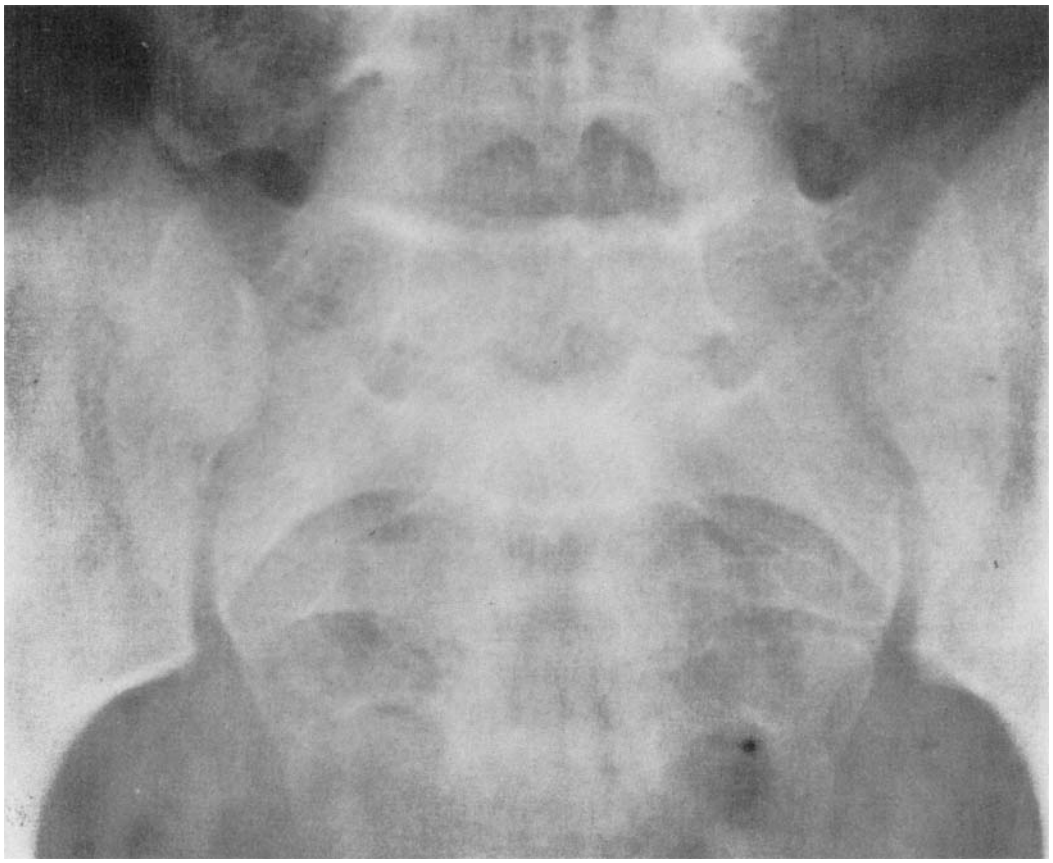

Fig 1. Sacroiliac joints in a normal 11-year-old boy. Note the normally wide interosseous spaces and the indistinct line of the subchondral plate.

been maintained in all, and actual functional loss has been minimal. Except for the spine and hips, important loss of mobility or usefulness of other joints has not been observed. No patient had destructive peripheral arthritis.

The majority of these patients were maintained only on salicylates. Treatment with phenylbutazone was limited to acute exacerbations. A course of radiation therapy was administered to one patient in 1953 for symptomatic relief when his pain and limitation of activity failed to respond to other measures.

DISCUSSION

Ankylosing spondylitis does not appear to be a rare cause of arthritis in children, even though not many reports of its occurrence have been published. In the experience of this clinic it represents approximately 7% of children seen for chronic arthritis. Scott emphasized, in 1942, a prespondylitic syndrome in adolescence which consisted of either symptoms of inflammatory disease in the spine or of peripheral arthritis (17). Lynn, in 1956, reported a case of ankylosing spondylitis in a 12-year-old child (18). Three male patients were de-

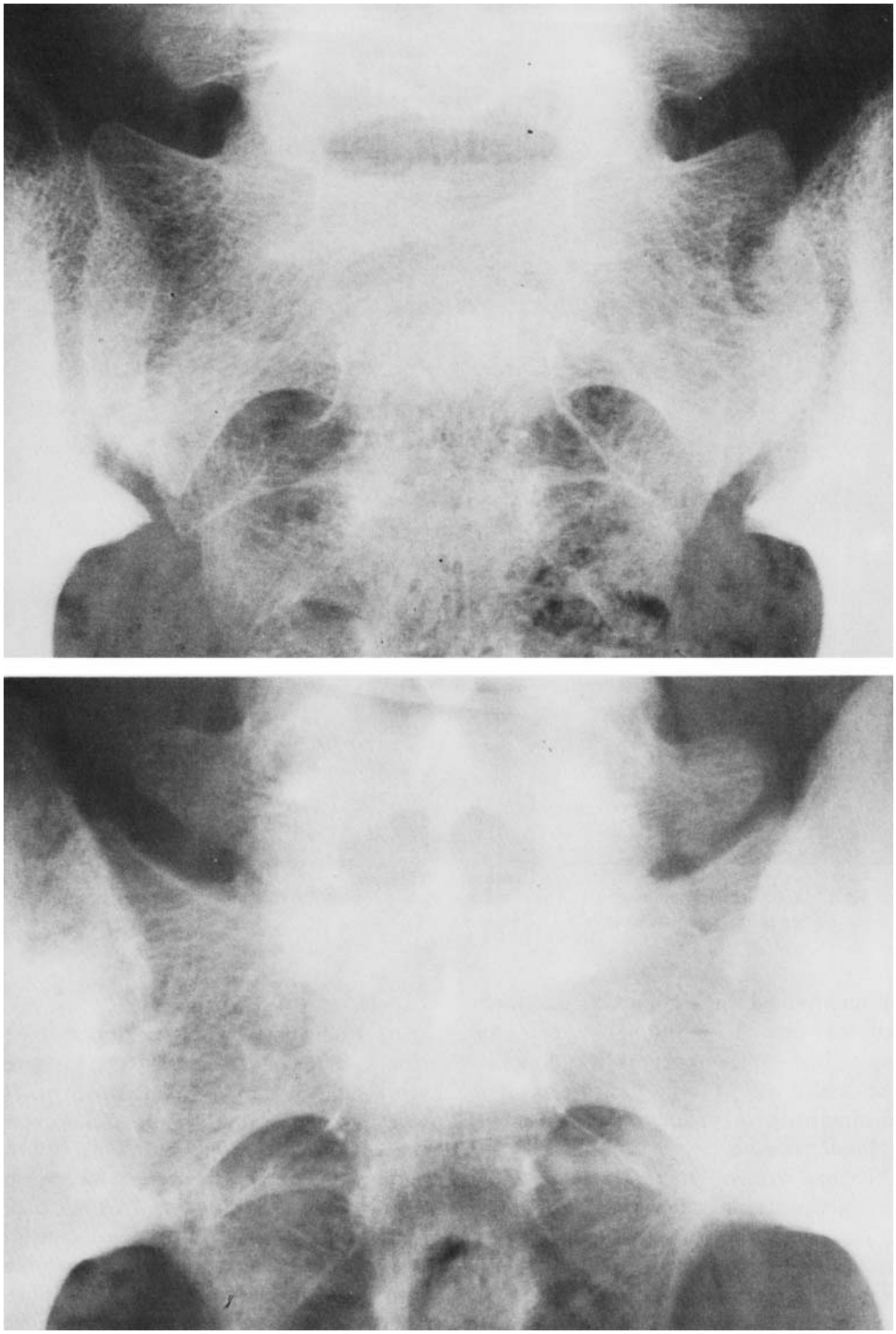

Fig 2 (left). Sacroiliac joints in a boy at age 11 shortly after onset of disease. Poor definition of the subchondral bone, especially on the left, and reactive sclerosis are consistent with the sacroiliac arthritis which occurs in ankylosing spondylitis. **(right).** Fourteen years later. Erosions and reactive sclerosis are more advanced and fusion is present on the left.

Table 4. Roentgenologic Abnormalities of the Sacroiliac Joints in Relation to Duration of Disease

Duration of disease (yr)	Number of patients with			Number of patients with films
	Erosions	Sclerosis	Fusion	
0–3	3	8	0	8
4–6	8	8	1	8
7–10	7	7	3	7
11–33	7	7	5	7
Total group at time of study	15	15	8	15

scribed by Edström *et al* in 1960 who had onset of arthritis at ages 5, 8 and 12 years, and subsequently developed typical features of ankylosing spondylitis (19).

Shaller *et al* (20) reviewed the case reports of 10 patients with childhood onset of ankylosing spondylitis (12, 18, 19, 21, 22) in 1969 and added 7 of their own. They emphasized that the diagnosis should be suspected in any child who is a male with onset of disease in late childhood, with symptoms referable to the sacroiliac joints or lumbodorsal spine, or with transient arthritis affecting only a few peripheral joints. Additional publications have appeared in the foreign literature (23–25).

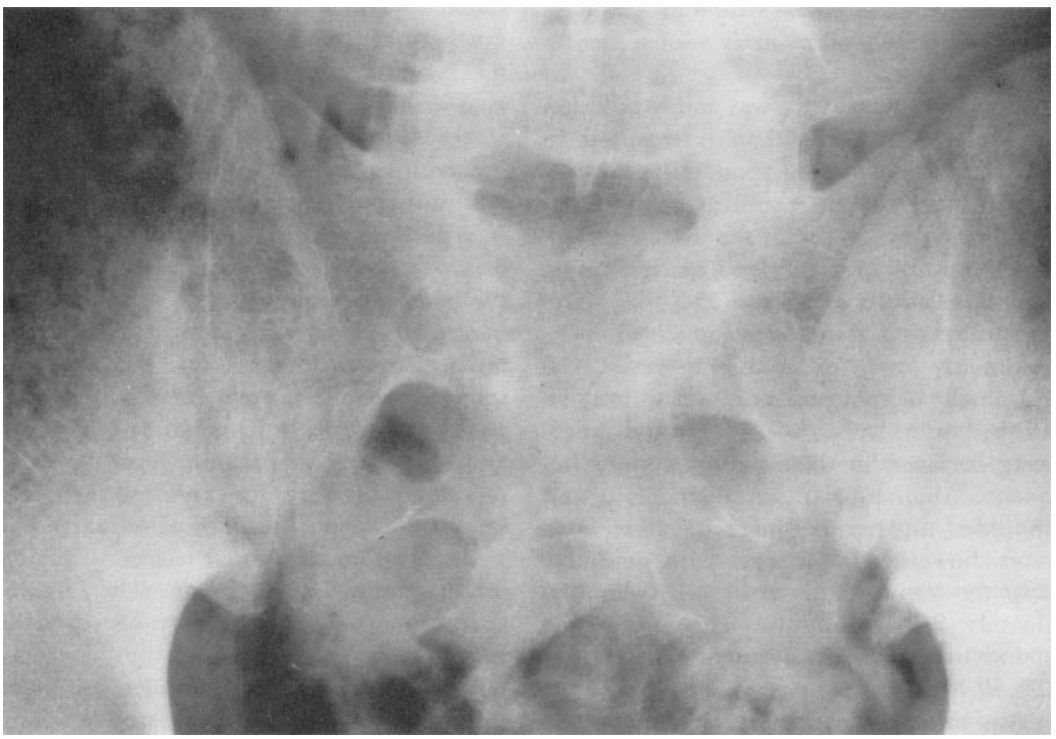

Fig 3. Sacroiliac joints in a 14 year old boy with polyarticular rheumatoid arthritis, rheumatoid nodules proven by biopsy and a strongly positive test for rheumatoid factors. Erosions are present and there may be minimal sclerosis. There were no syndesmophytes or squaring.

Table 5. Roentgenologic Abnormalities of the Lumbar Spine in Relation to Duration of Disease

Duration of disease (yr)	Number of Patients with				Number of patients with films
	Syndesmophytes	Squaring of the anterior vertebral bodies	Anterior marginal sclerosis (Shining corners)	Apophyseal joint disease	
0–3	0	0	0	0	4
4–6	0	0	0	1	2
7–10	2	2	1	2	6
11–33	3	3	1	1	6
Total group at time of study	5	5	2	4	15

Onset of ankylosing spondylitis in childhood is documented also in several large series of adults with the disease (26–31). In these papers, the initial symptoms could be traced to childhood or early adolescence in 6–10% of cases.

Extraspinal arthritis was more common in the present series than is reported in adults with ankylosing spondylitis (32–35). It was more common both at onset (57%) and during the course of the disease (93%). Forestier *et al* reported corresponding figures in adults of 23 and 73% (26). The weight-bearing joints were involved more commonly than in adults; however, the rhizomelic or root joints did not seem to be affected selectively. As an example, knees were involved in these children more frequently than hips or shoulders. Hip and shoulder involvement may be more common, however, in patients with onset before the young adult years (27). Approximately 25% of adults with ankylosing spondylitis have involvement of the hips (27, 30, 36, 37).

A significant feature in this study was relative sparing of the hands and wrists of these patients. Only one patient had transient involvement of a proximal interphalangeal joint. The occurrence of symptoms in the spine was delayed in half of the patients and progression of radiologic spinal disease was often inordinately slow. Furthermore, no patient had symptoms in the cervical spine prior to disease in the sacroiliac joints; and only 4 developed cervical spondylitis.

Sacroiliac arthritis was consistently the first radiographic abnormality of the spine. It is possible that the roentgenologic detection of sacroiliac arthritis may lag behind the clinical findings; usually the radiologic diagnosis can be suspected at the earliest onset of low-back symptoms. The sacroiliac joints appeared normal at onset in one patient in this series whose disease began in an ankle. The difficulty in detecting early sacroiliac arthritis in children is well-known, however, and films of the sacroiliac joints must be of optimal technical quality for diagnostic interpretation. The sacroiliac subchondral margins may be normally indistinct in this age group, but one does not expect to find reactive sclerosis. Indistinctness in the presence of reactive sclerosis suggests inflammatory disease.

The relationship between ankylosing spondylitis and juvenile rheumatoid arthri-

tis (38–39) has been one of confusion and controversy. The concept has been advanced that certain children with rheumatoid arthritis eventually develop ankylosing spondylitis (10, 21, 40, 41). Indeed, a striking incidence of sacroiliac abnormality has been reported in juvenile rheumatoid arthritis. Carter reviewed the earlier literature and found radiologic abnormalities of the sacroiliac joints in 23.7% of 202 patients diagnosed as juvenile rheumatoid arthritis (42). Ansell and Bywaters reexamined 149 of these patients 10 years after onset, however, and reclassified 7 of the 17 males who

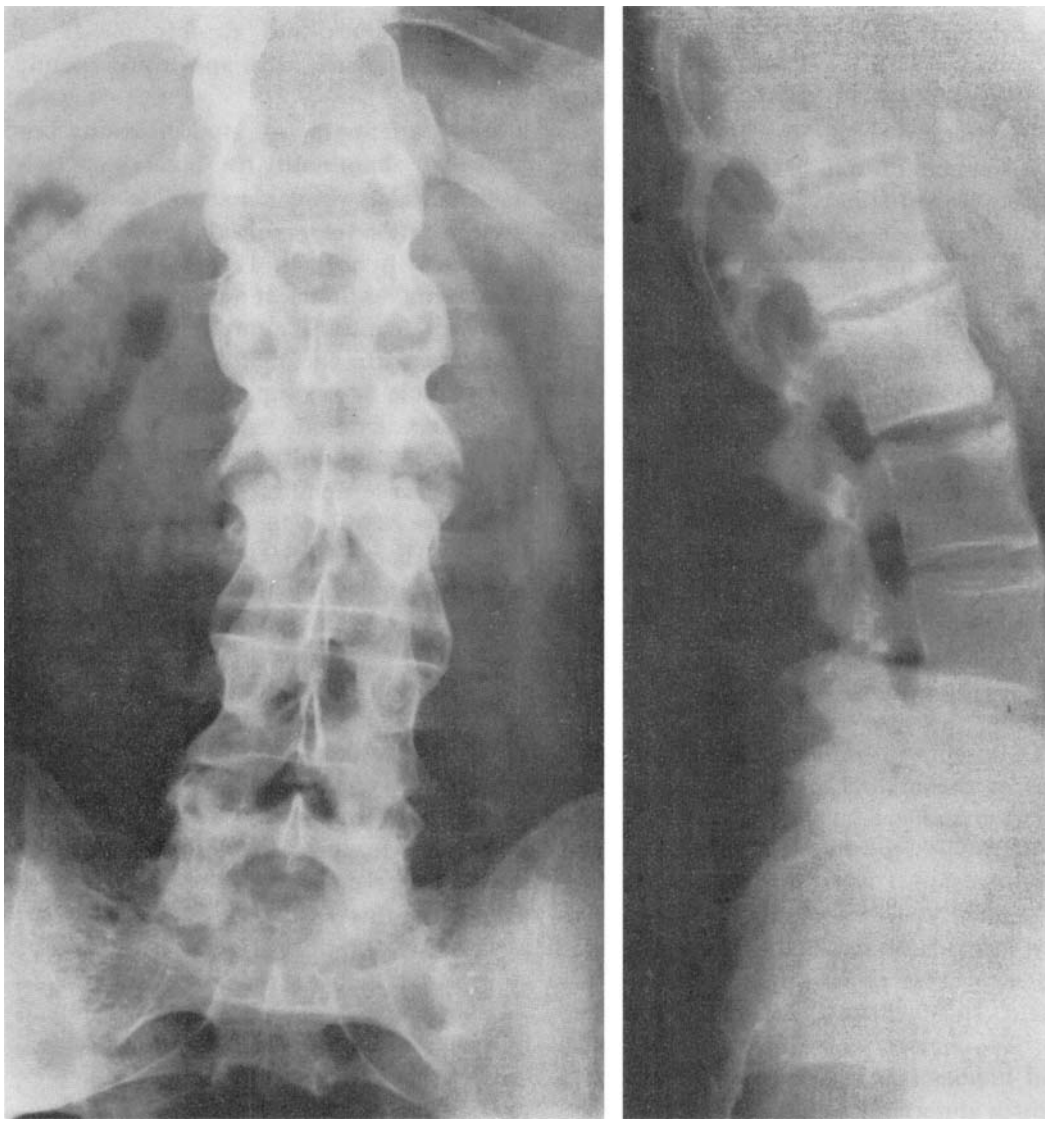

Fig 4 (left). Anteroposterior view. **(right).** Lateral view. Characteristic paraspinal ossification and squaring in a 36-year-old man in whom ankylosing spondylitis began at age 14.

Table 6. Functional Class at Time of Evaluation

Functional class	Number of patients	Duration of disease (yr)	
		Mean	Range
I	6	13	3–33
II	7	11	5–23
III	2	16	14–19
IV	0	—	—

had had abnormal sacroiliac joints as ankylosing spondylitis on the basis of further development of spinal abnormalities (43). In the present study, 2 of 26 patients with juvenile rheumatoid arthritis had sacroiliac abnormality but reactive sclerosis was not observed. Neither of these patients would have been diagnosed as ankylosing spondylitis.

It seems likely that reports of sacroiliac arthritis in any large number of children with juvenile rheumatoid arthritis reflects, in part, the difficulty early in the disease of excluding patients who will later develop diagnostic features of ankylosing spondylitis. When such a diagnosis is suspected, serial examinations and films of the sacroiliac joints will usually resolve the problem of classification within a 3-year period of time.

Children with either ankylosing spondylitis or rheumatoid arthritis frequently develop asymmetric extraspinal joint disease. Patients with juvenile rheumatoid arthritis may develop erosive peripheral joint involvement if early remission does not occur. Destructive arthritis of the hips is seen (45–46). Cervical spondylitis is more frequent (45, 50) than in ankylosing spondylitis. Apophyseal joint disease of the dorsal and lumbar spine may occur and result in growth abnormalities of the spine (45).

Children with ankylosing spondylitis exhibit a flat age-of-onset curve which probably represents the initial portion of the incidence curve for ankylosing spondylitis in general, with gradually increasing frequency through late adolescence and early adult years. In contrast, patients with juvenile rheumatoid arthritis have onset of disease usually at an earlier age (peak at 2–3 years). Uveitis in these children tends to be insidious and chronic (37, 47–49) rather than acute, as in ankylosing spondylitis.

Few patients in this study had any pronounced abnormality in laboratory tests. Hemoglobin, white blood cell count, and concentration of serum immunoglobulins were usually normal. Tests for rheumatoid factors and antinuclear antibodies were negative. In contrast, approximately 30% of patients with rheumatoid arthritis in a comparable age group would have a positive latex fixation test (2), and approximately 35% would have a positive test for antinuclear antibodies (44).

Twelve of these 15 patients had certain clinical characteristics which were helpful early in diagnosis: male sex, onset of arthritis 5 years of age or older, relative sparing of hands and wrists, a low incidence of cervical spine involvement, and negative tests for rheumatoid factors and antinuclear antibodies. In 208 patients with juvenile rheumatoid arthritis, 8 had these features in common. Two of these may actually represent ankylosing spondylitis but have not yet developed diagnostic features of this disease.

Prognosis in this series of patients with ankylosing spondylitis was relatively good in those who had early diagnosis and appropriate treatment. Hip disease was a serious problem in 3 patients. The other extraspinal joints were usually spared important functional limitation. No patient had striking growth retardation as may be seen

in juvenile rheumatoid arthritis or occasionally in ankylosing spondylitis of early onset (20).

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