Ankylosing Spondylitis in Shantou, China: 15 Years' Clinical Experience

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ABSTRACT. ***Objective.*** To study the clinical features of ankylosing spondylitis (AS) in Shantou, China, and assess the therapeutic effect of slow acting antirheumatic drugs (SAARD).

Methods. Clinical and laboratory data as well as the results of SAARD treatment were analyzed in 370 consecutive cases (46 female) seen in the period 1983–97. All patients met the modified New York criteria for AS. HLA-B27 was present in 83 of 89 (93.3%) patients tested.

Results. Insidious onset was seen in 94.3% of the cases studied: 33.5% with disease onset prior to age 20 years, 53.5% between ages 20–30 years, and 98.1% of all under age 40. Low back pain/discomfort, peripheral arthritis, positive "4" test, and tenderness over the sacroiliac joints/lumbar spine were the most frequent symptoms and signs. With some exceptions, the extent of sacroiliitis and involvement of the hip and spine were closely related to disease duration. Average disease duration was shorter among patients diagnosed after 1989 than before. A total of 107 cases have been followed for more than 3 years, of which 57 patients persisted with SAARD treatment for more than 3 years. Forty-four of the 57 cases (11.9% of the total of 370 cases) resulted in a good prognosis.

Conclusion. Early diagnosis of AS in Shantou, China, improved in the 1990s. SAARD were effective in the treatment of AS at least in a small portion of the patients. Patient compliance and longterm treatment were essential to obtain a better outcome. (J Rheumatol 2003;30:1816–21)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS CLINICAL FEATURES THERAPEUTIC RESPONSE
SLOW ACTING ANTIRHEUMATIC DRUGS

With the aim of improving the diagnostic level and treatment results for ankylosing spondylitis (AS), the clinical features, disease course, and therapeutic response of 370 consecutive cases of AS seen in Shantou, China, from 1983 to 1997 were studied.

MATERIALS AND METHODS

Patients. A total of 370 consecutive cases of definite AS seen in the rheumatology clinic of the First Affiliated Hospital of Shantou University Medical College from 1983 to 1997 were studied. All patients were natives of Shantou and their complete clinical data including case history, conventional radiography, and computer tomography (CT) scans were recorded.

Methods. Records of patients' histories, physical examinations, laboratory tests, and radiographs were analyzed. Spinal mobility was measured by spondylometer[1]. The "4" test was taken with the patient lying supine in flexion, abduction, and external rotation of the hips. The test would be positive if pain was elicited. Anteroposterior (AP) view radiographs of the pelvis and AP and lateral conventional radiographs of the lumbar spine were carried out for all patients. CT scans of sacroiliac joints were taken using an America PQ2000, whole body scan machine (window width/level = 550/1500 Hu). Radiographs and CT scans of sacroiliitis were graded according to the New York classification criteria for AS[2]. All patients fulfilled the Modified New York classification criteria for AS[3].

Management and followup. The major treatments before 1989 were nonsteroidal antiinflammatory drugs (NSAID) or low dose corticosteroids. Since then, therapy has included sulfasalazine and/or methotrexate and/or total glycoside of *Tripterygium wilfordii* Hook F (TwHF, an extract of the Chinese herb that is generally recognized as a SAARD in China)[4] plus NSAID or low dose corticosteroids (prednisone ≤ 10 mg/day). NSAID or low dose corticosteroid was discontinued after the patient's symptoms were relieved, while the SAARD were continued. Patients were followed-up every 1–3 months, and conventional radiography/CT scans were undertaken every 1–2 years.

Statistics. Clinical and laboratory data were analyzed using SPSS. Student t test was used for parametric comparisons, and the chi-square test for nonparametric comparisons.

RESULTS

Clinical manifestations at first visit. Among the 370 cases, 324 were male and 46 female (male:female 7:1), mean age 29.5 years (range 12–50 yrs), mean age at disease onset 22.4 years (range 7–45), and mean disease duration at the time of diagnosis was 7.1 years (range 0.25–36). The mean age at disease onset for women was 24.2 years, older than the 22.1 years in men. Disease duration was similar in both sexes.

As shown in Table 1, 33.5% of the patients had their disease onset prior to age 20, 53.5% at 20–30 years of age, and 98.1% before 40 years of age. In 94.3% of the patients the disease onset was insidious, i.e., the symptoms were mild and appeared gradually, and were often neglected by the patient; 13.5% of the cases had history of injury such as a fall, sprain, or bump and it was after a period of time that the symptoms slowly began to appear. Before AS was diag-

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Table 1. Manifestations at first visit of 370 outpatients with AS.

Clinical Features	Positive/total (%)	Clinical Features	Positive/total (%)
Disease onset		Night pain	266/370 (71.9)
Acute	21/370 (5.7)	Morning stiffness duration > 15 min	214/370 (57.8)
Insidious	349/370 (94.3)	Relief after activity	192/370 (51.9)
Onset age, yrs		Neural symptoms over lower limb	21/370 (5.7)
< 20	124/370 (33.5)	Sciatic nerve pain	8/370 (2.2)
20–30	198/370 (53.5)	Lower limb pain	13/370 (3.7)
< 40	363/370 (98.1)	Signs	
Sex, M:F	7:1	"4" test (+)	323/370 (87.3)
Family history	28/370 (7.6)	Tenderness over SIJ	338/370 (91.4)
Injury history	50/370 (13.5)	Tenderness over lumbar spine	343/370 (92.7)
Symptoms		Flexion range of spine < 40°	186/370 (50.3)
Axial joint	221/370 (59.7)	Chest expansion ≤ 2.5 cm	149/370 (40.3)
Lumbar	214/370 (57.8)	Distance from finger to floor > 0	307/370 (83.0)
Back	3/370 (0.8)	Distance from occipitals to wall > 0	117/370 (31.6)
Cervical	2/370 (0.5)	Extraarticular manifestation	
Chest	2/370 (0.5)	Iritis or history of iritis	17/370 (4.6)
Girdle joint	34/370 (9.2)	Arrhythmia	7/370 (1.9)
Hip	33/370 (8.9)	Apical pulmonary fibrosis/ cavitations	6/370 (1.6)
Shoulder	1/370 (0.3)	Arachnoid diverticula	3/370 (0.8)
Peripheral arthralgia	92/370 (24.9)	History of diarrhea (> 1 yr)	3/370 (0.8)
Lower limb	71/370 (19.2)	Urogenital	3/370 (0.8)
Knee	27/370 (7.3)	Laboratory tests	
Ankle	5/370 (1.4)	ESR > 20 mm/h	250/363 (68.9)
Foot	5/370 (1.4)	CRP > 8 mg/l	143/278 (51.4)
Heel	14/370 (3.8)	WBC > 10×10^9	50/285 (17.5)
Polyarticular	20/370 (5.4)	IgG > 16.0 g/l	83/215 (38.6)
Upper limb	2/370 (0.5)	IgA > 3.3 g/l	48/215 (22.3)
Hand	2/370 (0.5)	IgM > 2.2 g/l	49/215 (22.8)
Upper and lower limb	19/370 (5.1)	HLA-B27 (+)	83/89 (93.3)

nosed, disc problems or other mechanical disorders had been ruled out for these patients. Low back pain as the first manifestation was seen in 57.8% of cases and peripheral arthralgia in 24.9%. Only one case complained of shoulder pain at his first visit. Among the 107 cases that have been followed for more than 3 years, 11 (11/107, 10.3%) cases complained of shoulder pain during the course of followup. Night pain was reported in 71.9% and morning stiffness in 57.8% of the patients. Positive "4" test and tenderness over the sacroiliac joints and lumbar spine were the most common physical signs.

Extraarticular manifestations. History (or evidence) of iritis was recorded in 4.6% of the patients. Heart, lung, gastrointestinal, and urogenital involvement was uncommon (Table 1). One case had spinal myelography conducted by a neurosurgeon before coming to my clinic, and 3 cases of arachnoid diverticula were found at the level of the sacral vertebra 1–2.

Radiography. Grade II, III, and IV radiological changes of sacroiliitis accounted for 32.8%, 38.6%, and 28.6% of cases, respectively (Table 2). The rate of grade II sacroiliitis in women was higher than in men (50.9% vs 27.5%), while grade IV sacroiliitis in women was lower than in men (14.6% vs 30.4%). The involvement of hip joint, "bamboo" spinal changes, ligament calcification, squaring of vertebra, and facet joint obliteration was seen in 14.6%, 20.8%, 7.3%, 17.3%, and 40.0% of patients, respectively.

Relationship between sacroiliitis, hip involvement, spinal changes, and disease duration. As shown in Table 2, grading of radiological changes of sacroiliitis increased with disease duration. The involvement of hip joints and spine also increased with disease duration. Nevertheless, during the period 1990–97, there were 65 cases whose CT scans of the sacroiliac joint revealed grade II changes, and among these 65 cases, the male:female ratio was 3:1 and age of onset varied from 11 to 32 years, of which 19 cases could be classified as juvenile onset. Disease duration at the time of diagnosis ranged from 3 months to 16 years (average 4.1 yrs). Among the 65 cases, 31 had the disease for more than 3 years, 12 cases more than 8 years, and 3 more than 15 years. Among the 19 patients with AS of juvenile onset, 10 had disease duration at time of diagnosis of over 3 years, and 3 over 9 years (Table 3). It appeared that, aside from a higher female ratio, no distinct features of disease duration or age of disease onset existed in these 65 cases with grade II sacroiliitis.

Table 2. Relationship between the involvement of hip, spine, grade of sacroiliitis, and disease duration.

Radiographic Grade	Sacroiliitis		Hip Involvement		Bamboo Spine	
	N (%)	ADD, yrs	N (%)	ADD, yrs	N (%)	ADD, yrs
II	121 (32.8)	4.4	4 (3.3)	3.5	9 (7.4)	7.6
III	143 (38.6)	6.3	21 (14.7)	7.4	15 (10.5)	9.7
IV	106 (28.6)	11.2	29 (27.4)	10.3	53 (50.0)	12.8
Total	370 (100.0)	7.1	54 (14.6)	8.7	77 (20.8)	11.6

ADD: average disease duration.

Table 3. Distribution of disease duration, onset age, and sex in 65 cases of grade II CT sacroiliitis.

Disease Duration, yrs	No.			Age of onset, yrs			
	Male	Female	Total	< 16	16–30	> 30	Average
~ 1	14	4	18	3	13	2	23.3
~ 2	7	3	10	2	8	0	20.3
~ 3	4	2	6	1	5	0	21.8
~ 4	4	0	4	4	0	0	14.0
~ 5	7	1	8	3	3	2	23.0
~ 6	2	0	2	1	1	0	18.5
~ 7	1	0	1	0	1	0	30.0
~ 8	3	1	4	2	2	0	17.8
~ 9	1	2	3	3	0	0	12.3
~ 10	3	2	5	0	4	1	28.0
> 10	3	1	4	0	4	0	22.0
Total	49	16	65	19	41	5	20.8

The incidence of hip involvement among the juvenile cases did not increase with disease duration. In the 1980s, the rate of hip joint involvement in the patients with grade II and III sacroiliitis was higher than that in grade IV sacroiliitis. Nevertheless, almost all "bamboo" spinal changes were found in patients with grade IV sacroiliitis, i.e., in those with long disease duration (Table 4).

Change of age of onset and disease duration during 15 years. Although the difference is of no statistical significance, both the average age of disease onset and the disease duration at the time of diagnosis seem to be decreasing. Average disease duration at the time of diagnosis in the whole group was 7.1 years; it was 8.1 years in the 1980s and 6.5 years in the 1990s.

Followup. Of the 370 patients, one died from an atlantoaxial fracture and another died from cancer. No serious adverse drug reactions were noted, except 2 cases with mild hemorrhage of the upper digestive tract. No childbirth with congenital disease was noted during the course of followup.

Among the whole group of 370 patients, 107 (28.9%) cases were followed for more than 3 years, out of which 57 patients (15.4% of the total) persisted in taking SAARD therapy for more than 3 years; 44 of the 57

Table 4. Comparison of hip, spine involvement, and degree of sacroiliitis in juvenile AS during the 1980s and 1990s.

	1980s (25 Cases)				1990s (76 Cases)			
	Sacroiliitis		Hip Inv.	Bamboo Spine	Sacroiliitis		Hip Inv.	Bamboo Spine
	N (%)	ADD, yrs	N (%)	N (%)	N (%)	ADD, yrs	N (%)	N (%)
Grade								
II	5 (20)	2.8	3 (60)	0	24 (31.6)	4.8	3 (12.5)	0
III	10 (40)	7.9	5 (50)	1 (10)	36 (47.4)	6.3	8 (22.2)	0
IV	10 (40)	12.4	4 (40)	2 (20)	16 (21.0)	10.9	6 (37.5)	7 (43.7)
Total	25 (100)	8.7	12 (48)	3 (12)	76 (100)	6.8	17 (22.4)	7 (9.2)

ADD: average disease duration; Hip Inv.: hip involvement.

patients (11.9% of the total 370 cases) showed good outcome at the end of last followup, with symptoms relieved and all laboratory abnormalities returned to normal, and experiencing good health in activities of daily life that lasted for at least one year, even though NSAID might occasionally be used.

The results of radiological followup in 107 cases are shown in Table 5, out of which 40 cases (37.4%) showed no changes from baseline status. New spinal involvement was found in 30 cases (28.0%). At baseline, the percentage of grade II sacroiliitis in the 44 patients with good outcome was significantly higher (52.3%) than in the others (31.7%; $p < 0.05$); whereas the percentage of spinal involvement was significantly lower than in the others (9.0% vs 28.6%; $p < 0.05$). The percentage of grade III and IV sacroiliitis was also lower in the group with good outcome, although not statistically significant. At the endpoint, 26 of the 44 patients with good outcome (59.1%) showed that radiological changes remained at baseline status, which was significantly higher than in the others (22.2%); only one case showed new spinal involvement, which was distinctly lower than in the others (2.3% vs 23.8%).

The changes in clinical features and laboratory results during the course of followup are shown in Table 6. Night pain, morning stiffness, chest expansion, and erythrocyte sedimentation rate (ESR) were improved in most of the patients, whereas finger-to-floor distance, lumbar anterior flexion, and occipital-wall distance showed no appreciable improvement. At baseline, the average range of chest expansion in the good outcome group was significantly greater than in the others, with all other disease measures also being milder. At endpoint, aside from occipital-wall distance, all other measures were significantly improved.

DISCUSSION

Twenty years ago, it was believed that AS was less common in China. Today, it is clear that AS is one of the common rheumatic diseases seen in China[5], with a prevalence similar to that reported in studies of Caucasians[6].

Ten years ago, a clinical comparison of AS was carried out between Chinese (150 cases from Shantou in southeast China, Beijing in north China, and Shenyang in northeast China) and Americans (131 cases from Stanford University Medical Center, Stanford, California)[7]. It was found that the clinical features were similar between these 2 groups, but the incidences of large joint pain of lower limbs, limitation of lumbar spine mobility, decrease of thoracic expansion, elevated ESR, and radiographic sacroiliitis changes greater than grade 3 were statistically higher in the Chinese group. The incidences of pain of small joints such as wrist, finger and toe, iritis, radiographic spinal involvement, and hip joint abnormalities were statistically higher in the American group[7].

In the present study, the incidence of iritis or history of iritis was 4.6%, higher than in our previous study of the Chinese group (2.0%), but it remains lower than in the American patients (7.7%)[7]. Whether this is related to genetic differences awaits further study. The incidences of hip, knee, and ankle involvement in the present study were much lower than in the previous study, lower than both the Chinese group from northern China and the American group. This result was in agreement with the result of our previous ILAR–China study[5], and was later confirmed by the APLAR study[8]. It is postulated that this might be a special feature of patients in the Shantou area. Similar phenomena may also explain the low incidence of shoulder pain (0.3%) in the present study. Nevertheless, there were 11 cases among the 107 patients followed for over 3 years who

Table 5. Radiological outcome of the 107 cases of AS with followup for more than 3 years.

	Grade of Sacroiliitis			Spinal Involvement	Peripheral Arthritis	Total, N (%)
	II	III	IV			
Total, N = 107						
Baseline, n (%)	43 (40.2)	37 (34.6)	27 (25.2)	22 (20.6)	55 (51.4)	
Endpoint, n (%)	14 (13.1)	29 (27.1)	64 (59.8)	38 (35.5)	9 (8.4)	
Unchanged, n (%)	14 (32.6)	12 (32.4)	7 (25.9)	7 (31.8)		40 (37.4)
Good outcome, N = 44						
Baseline, n (%)	23 (52.3)	13 (29.5)	8 (18.2)	4 (9.0)	26 (59.0)	
Endpoint, n (%)	12 (27.3)	12 (27.3)	20 (45.4)	5 (11.4)	0	
Unchanged, n (%)	12 (52.2)	6 (46.2)	4 (50)	4 (100)		26 (59.1)
Others, N = 63						
Baseline, n (%)	20 (31.7)	24 (38.1)	19 (30.2)	18 (28.6)	29 (46.0)	
Endpoint, n (%)	2 (3.2)	17 (27.0)	44 (69.8)	33 (52.4)	9 (14.3)	
Unchanged, n (%)	2 (10.0)	6 (25.0)	3 (15.8)	3 (16.7)		14 (22.2)
P (good vs others)						
Baseline	$0.01 < p < 0.05$	> 0.05	> 0.05	$0.01 < p < 0.05$	> 0.05	
Unchanged	< 0.01	> 0.05	> 0.05	> 0.05	< 0.01	< 0.01

Table 6. Clinical status of the 107 cases with followup for more than 3 years.

	Total, N = 107	Good Outcome, N = 44	Others, N = 63	p (Good vs Others)
Night pain				
Baseline, n (%)	92 (86.0)	36 (81.8)	56 (88.9)	> 0.05
Endpoint, n (%)	18 (16.8)	1 (2.3)	17 (27.0)	< 0.01
p	< 0.01	< 0.01	< 0.01	
Morning stiffness time, mean ± SD, h				
Baseline	2.95 ± 4.38	2.13 ± 3.71	3.53 ± 4.71	0.11
Endpoint	1.59 ± 3.78	0.03 ± 0.09	2.59 ± 4.57	< 0.01
p	0.03	< 0.01	0.29	
Finger–floor distance, mean ± SD, cm				
Baseline	19.99 ± 17.79	18.49 ± 17.29	21.13 ± 18.07	0.48
Endpoint	17.06 ± 16.96	10.05 ± 12.53	23.02 ± 17.92	< 0.01
p	0.26	0.02	0.60	
Spine anterior flexion, mean ± SD, degrees				
Baseline	36.96 ± 16.45	38.95 ± 14.81	35.51 ± 17.41	0.30
Endpoint	40.60 ± 17.11	49.02 ± 13.53	33.70 ± 16.64	< 0.01
p	0.14	< 0.01	0.59	
Chest expansion range, mean ± SD, cm				
Baseline	3.71 ± 1.68	4.48 ± 1.41	3.16 ± 1.65	< 0.01
Endpoint	4.54 ± 1.81	5.50 ± 1.57	3.72 ± 1.58	< 0.01
p	< 0.01	< 0.01	0.08	
Occipital–wall distance, mean ± SD, cm				
Baseline	3.37 ± 5.20	2.93 ± 4.11	3.71 ± 5.89	0.50
Endpoint	3.86 ± 5.49	1.81 ± 2.84	5.50 ± 6.46	< 0.01
p	0.56	0.18	0.17	
ESR, mean ± SD, mm/h				
Baseline	41.64 ± 30.33	38.11 ± 26.91	44.23 ± 32.36	0.31
Endpoint	23.39 ± 21.23	14.37 ± 13.22	30.39 ± 23.50	< 0.01
p	< 0.01	< 0.01	0.01	

showed shoulder pain (10.3%), similar to the incidence among Westerners with AS[9].

The use of advanced radiological technology, such as CT and magnetic resonance imaging, has much improved the early diagnosis of AS. In this study, patients' disease duration at first diagnosis in the 1990s was shorter than that in the 1980s (6.5 vs 8.1 yrs), and the percentage of radiological grade II and grade III sacroiliitis was also higher than in the 1980s. In contrast, the percentage of grade IV radiological sacroiliitis and cases of spinal involvement were decreased in the 1990s. These improvements apparently were due to the use of modern technology such as CT scans in the early diagnosis. That average disease duration at the time of diagnosis in the 1990s was still more than 6 years indicates that much effort must be made to further improve the early diagnosis.

As one kind of chronic progressive disease, there is currently no medical treatment for AS. In this study, only 28.9% (107/370) of the patients were followed for more than 3 years. The overall percentage of patients having consistent treatment over 3 years was only 15.4% (57/370), indicating patients' lack of confidence in treatment in general and the importance of patient compliance.

As for the therapy, there is a lack of generally accepted disease modifying treatment. Even for SAARD such as sulfasalazine, methotrexate, and TwHF, the therapeutic effects remain controversial[4,10,11]. The details of our experience in the treatment of AS will appear in a separate report. Our preliminary impression is that at least a small portion of patients with AS benefited through at least 3 years' continual treatment. Whether this resulted from the therapy or was due to a benign course of the disease per se, or even due to a "monocyclic" disease pattern as may appear in rheumatoid arthritis, awaits further exploration.

The clinical features of our patients indicating good prognosis include: (1) relatively mild disease severity as exemplified by lower grade radiological sacroiliitis, absent or low spinal involvement, mild functional impairment, and slight laboratory abnormalities; and (2) good patient compliance in persisting with treatment for more than 3 years. In summary, it is the author's view that early diagnosis and longterm (more than 3 years) treatment are essential for AS to have a good outcome.

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