The Natural History of Ankylosing Spondylitis as Defined by Radiological Progression

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ABSTRACT. ***Objective***. Radiological status is an important objective endpoint in the assessment of ankylosing spondylitis (AS). We investigated the disease development of AS using radiological change.

Methods. The existing radiographs (n = 2284) of 571 AS patients attending the Royal National Hospital for Rheumatic Diseases were scored retrospectively using the Bath Ankylosing Spondylitis Radiology Index. (1) Progression of disease was initially examined cross sectionally. Univariate analysis was used to examine factors associated with joint involvement. (2) Progression of disease was then examined longitudinally for patients with films at time of symptom onset. (3) Rate of progression of radiological change was calculated using longitudinal data of 2 sets of radiographs taken 10 years apart (patient number = 54). The results from this were used to extrapolate backwards to age at first radiological change.

Results. (1) Progression to cervical spine disease was a function of: disease duration, severity of hip and lumbar involvement, and a history of iritis ($p < 0.001$). Lumbar involvement was associated with disease duration, age now, and severity of cervical and hip involvement ($p < 0.001$). Hip involvement was a marker for cervical disease and associated with disease duration ($p < 0.001$). (2) Longitudinal analysis revealed marked variation among patients with a slow general rate of progression. (3) The progression of AS over any 10 year period is linear [first 10 years = 30% (SD 0.3) of potential change, 10-20 yrs = 40% (SD 0.3) change, 20–30 yrs = 35% (SD 0.4) change ($p = 0.5$)]. Backward extrapolation suggests that the approximate time of first radiological change is at the age of 8 years.

Conclusion. (1) AS is a linearly progressive disease with about 35% change every 10 years. Spinal involvement is largely an expression of disease duration while the hips become involved in about 25% of individuals and may predict a more severe outcome for the cervical spine. (2) Backward extrapolation shows that the disease process may start as young as 8 years of age. However, the time interval between the disease trigger and radiological change remains unknown. (J Rheumatol 2002;29:1236–43)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS RADIOLOGY DISEASE HISTORY BASRI

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disorder involving the sacroiliac (SI) joints, the spine, and often the hips or peripheral joints. Characteristic radiographic changes of AS begin in the SI joints and evolve slowly over many years to involve the rest of the spine[1]. However, the natural history of the disease is poorly understood. A number of measures have been used simultaneously to monitor disease outcome[2-6]. However, radiographs have the advantage over other measures in being objective and uncomplicated by diurnal variation. Radiographic damage is irreversible and thus reflects the cumulative natural history of disease in the individual patient.

Recently the Bath Ankylosing Spondylitis Radiology Index (BASRI-total) was developed to allow the scoring of radiological change for the spine and hip in AS[7,8]. It grades the SI joints, hips, lumbar spine (lateral and anteroposterior), and cervical spine on a scale of 0–4. Using BASRI to examine the natural history and radiographic progression of AS will make possible studies into the influence of external factors (i.e., environmental factors) on the rate of disease development and on the course of AS.

Our aim was to (1) examine the progression of disease cross sectionally as well as factors associated with hip, lumbar, or cervical involvement; (2) examine the longitudinal progression of disease among individuals in whom a diagnosis was made and radiographs taken within 2 years of developing symptoms; and (3) examine the rate of radiological change and estimate by backward extrapolation the age at which first radiological change may occur. Assuming rate

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of progression before symptom onset is equal to rate of progression after symptom onset, then extrapolation can indicate age of first radiological change.

These 3 approaches were designed to reflect the disease history of AS, including first radiological change, rate of progression, variation among individuals, and factors determining this variation.

MATERIALS AND METHODS

All existing radiographs (years 1975-2001) of AS patients (i.e., retrospective examination) attending the Royal National Hospital for Rheumatic Diseases were randomly scored using BASRI by 2 trained independent readers (SB, AAl-S). [Intra and interobservations from the validation of BASRI (i.e., hip, SI joint, lumbar and cervical spine separately) ranged between 75-86% (intra) and 73-79% (inter)[7] and variations among readers SB and AAl-S ranged between 77%-89% (intra) and 74%-88% (inter)]. Discrepancies between scores were rescored by a third and fourth trained reader (KM, AC) and a consensus was reached. The BASRI grades lumbar and cervical spine and hips on a scale of 0–4. A minimum of grade 2 in terms of sacroiliitis is needed to diagnose AS. Thus the scale ranges between 2–16. Patients were selected if they had been diagnosed according to the New York Criteria (definite AS), had full sets of radiographs (i.e., a complete set according to the BASRI, consisting of neck, lumbar, pelvis, and hip radiographs), and complete notes (including patient reported age at first symptom onset, disease duration, family history, etc.). Where more than one set of radiographs was available, a random number table was used to select the set for inclusion in the cross sectional database.

1. Cross sectional progression of AS (n = 571 patients with 4 radiographs per patient or 2284 radiographs). A plot was made of the percentage of patients with regional involvement (lumbar, cervical, and hip) at each year of disease duration. A cutoff of grade 2 or more (i.e., mild disease) on the BASRI scale was used to define involvement of the joint. Univariate analysis was used to examine factors such as: secondary diseases (psoriasis, iritis, inflammatory bowel disease, diagnosis taken from medical notes of patients), delay in diagnosis of AS (time between first symptoms and diagnosis, chosen as a factor because a diagnosis may encourage the patient to exercise and this may aid in delaying fusion or other changes), age, age of symptom onset, family history (patient self-report in the medical notes), current disease activity (Bath Disease Activity Index, BASDAI[8]: a 10 point scale assessing fatigue, pain, morning stiffness, tenderness, and discomfort), disease duration, and sex, which are associated with cervical, hip, and lumbar involvement. Multivariable analysis was performed using these factors.

2. Longitudinal progression of AS. Patients with radiographs taken within 2 years of symptom onset (n = 20) and who had more than one set of radiographs were selected. The BASRI score was plotted against disease duration.

3. Rate of progression and backward extrapolation to time of first radiological change. Patients with 2 sets of radiographs taken 10 years apart were selected. Patient radiographs taken at 0-2, 10 (± 2), and 20 years (± 2) from time of symptom onset were used to examine rate of progression of disease over any 10 year period. To remove the ceiling effect the progression rate was calculated, not in relation to total score, but in relation to remaining score. The formula to calculate relative progression (i.e., the score change per amount of score available to change[9]) was:

$$\frac{\text{(score of designated year)} - \text{(score of previous year)}}{\text{total score (16)} - \text{(score of previous year)}}$$

Using this estimate of rate of progression of radiological change, an extrapolation to time of first radiological change was performed. Assuming rate of progression before symptom onset is equal to rate of progression after symptom onset, then extrapolation can indicate age of first radiological change. (However, this method does not tell us the rate of progression in a given patient before and after the interval studied).

Statistical methods. SPSS v. 10 was used for the analysis of variance (univariate and multivariable analysis.)

RESULTS

Demographic data are shown in Table 1.

1. Progression of disease. The cross sectional data of all 571 patients was plotted against disease duration (Figure 1, Tables 2 and 3). More patients had lumbar involvement than cervical disease at all points in the disease duration ($p < 0.001$) and 86% of those with cervical disease also had lumbar spine changes. Those patients with cervical changes alone (i.e., no lumbar involvement, 14%) had a shorter disease duration [18 yrs (SD 10) vs 23 yrs (SD 10), respectively ($p = 0.006$), mean difference 5 (confidence interval, CI, 1.5-8.9)] than those with both lumbar and cervical change. After 25 years of disease, about 75% of patients had cervical spine involvement and 85% lumbar spine involvement.

Multivariate analysis showed the factors associated with amount of cervical involvement include (Table 3): disease duration, degree of hip disease, degree of lumbar spine disease, and history of iritis. A model of these factors explains 59% ($p < 0.0001$) of the variation seen in cervical spine involvement. The factors associated with degree of lumbar spine disease were: disease duration and level of cervical involvement. A model of these factors explains 36% ($p < 0.0001$) of the variation seen in lumbar spine involvement. Only degree of cervical spine involvement and disease duration were associated with level of hip disease, describing 19% ($p < 0.0001$) of the variation seen in level of hip disease. Factors not associated with progression to lumbar, cervical, or hip disease include: disease activity (BASDAI), delay in diagnosis, family history, bowel disease, and presence of psoriasis.

2. Longitudinal progression. Individual plots of patients with radiographs taken within 2 years of symptom onset show there is marked variation in radiological score among individual patients (Figure 2). There is a slow general rate of progression, with some individuals having bursts of rapid change. However, these periods of change can occur at any time in the course of disease. The stage when patients first report symptoms does not appear to show a relationship to the time when the disease process may begin. In 11 of the 20 (55%) subjects, there was a score of more than 4 in the BASRI. Thus, for these patients there was involvement of the SI joints (which would score from 2–4) and additional areas such as the lumbar spine, neck, or hips before showing any symptoms of disease. In 5 (25%) individuals there was a score of 8 or more, suggesting SI joint disease and moderate or severe neck/lumbar or hip disease without symptoms.

3. Rate of progression and extrapolation to age at first

Table 1. Demographic data.

Disease duration, yrs	Mean 20 (SD 10.6); median 19; range 0–64
Age, yrs	Mean 43 (SD 11.0) ; median 42; range 17–80
Age at onset, yrs	Mean 23 (SD 8.0); median 22; range 10–56
Male, % (no.)	79 (403/507)
Peripheral involvement, % (no.)	47 (235/500)
Iritis, % (no.)	38 (188/497)
IBD, % (no.)	9 (42/504)
Psoriasis, % (no.)	19 (92/492)

Total no. of radiographs*	
No. of subjects, n	661
Sacroiliac joints, n	1039
Lumbar spine, n	977
Cervical spine, n	914
Hips, n	979

	Cross Sectional Analysis	Longitudinal Analysis	
		From Time of Onset	Rate of Change
No. of subjects, n	571	20	54
Sacroiliac joints, n	571	61	108
Lumbar spine, n	571	61	108
Cervical spine, n	571	61	108
Hips, n	571	61	108

* Patients without and with complete BASRI score.

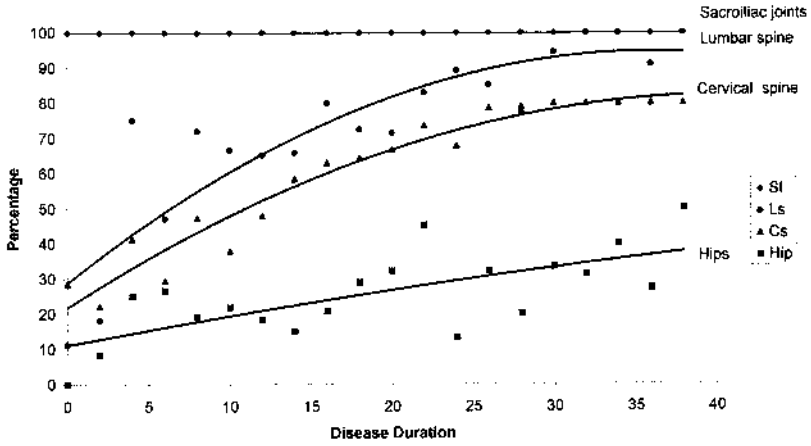

Figure 1. Percentage of patients with regional involvement (hip, cervical, lumbar) against disease duration.

radiological change. On a BASRI scale of 2–16 the change in score at disease duration time points of 0–10, 10–20, and 20–30 years (Table 4) was 2.9 (± 3), 3.1 (± 2.5), and 1.6 (± 1), respectively. There was no significant difference between rate of radiological progression in these 3 time periods (p = 0.163).

If, to remove the ceiling effect, the progression rate is calculated not in relation to total score but to remaining score, the progression rate is 30% (of remaining change) (SD 0.3), 40% (of remaining change) (SD 0.3), and 35% (of remaining change) (SD 0.4) at time points 0–10, 10–20, and 20–30 years, respectively. Thus, the rate of radiological change is linear (Figure 3).

Demographic data shows that of the 7 patients who progressed more than the mean + 1 SD, all were men, average age was 35 years, age of onset was 19 years, 6/7 had iritis (85%), 4/7 (57%) had a diagnosis of peripheral involvement, and they exercised an average 2.4 h/week.

Table 2. Number of patients with regional involvement (hip, lumbar spine, cervical spine).

Disease Duration, yrs	No. of Patients	Lumbar Spine (%)	Cervical Spine (%)	Hips (%)
0 to 5	53	20 (38)	13 (25)	5 (9)
6 to 10	75	42 (56)	24 (32)	12 (17)
11 to 15	88	52 (59)	41 (47)	15 (17)
16 to 20	102	72 (71)	59 (58)	24 (24)
21 to 25	95	72 (76)	62 (65)	25 (26)
26 to 30	68	56 (82)	48 (71)	19 (28)
31 +	90	80 (89)	62 (69)	26 (29)

Table 3. Factors associated with progression to cervical spine, lumbar spine, or hip involvement.

	Factors Associated with Cervical Spine		Factors Associated with Lumbar Spine		Factors Associated with Hip	
	Correlation	Univariate Analysis	Correlation	Univariate Analysis	Correlation	Univariate Analysis
Disease duration	0.3	p < 0.0001	0.4	p < 0.0001	0.2	p = 0.005
Age now	0.3	p < 0.001	0.4	p < 0.0001	0.02	
BASDAI	–0.02		–0.05		0.05	
Age at symptom onset	0.02		0.03		–0.09	
Delay in diagnosis	0.1		0.01		–0.1	
	Mean (SD)	Univariate Analysis	Mean (SD)	Univariate Analysis	Mean (SD)	Univariate Analysis
Family history, N = 413, 158*	Neg = 2.1 (1.7), Pos = 1.8 (1.7)		Neg = 2.4 (1.5), Pos = 2.2 (1.4)		Neg = 0.7 (1.2), Pos = 1.0 (1.2)	
Hip disease, N = 418, 153*	Neg = 1.7 (1.6), Pos = 3.3 (1.5)	p < 0.0001	Neg = 2.1 (1.5), Pos = 3.0 (1.4)	p < 0.0001		
Cervical spine disease, N = 209, 362*			Neg = 1.1 (1.4), Pos = 2.2 (1.4)	p < 0.0001	Neg = 0.1 (0.7), Pos = 0.5 (1.4)	p < 0.0001
IBD, N = 523, 48*	Neg = 2.1 (1.7), Pos = 1.5 (1.7)		Neg = 2.4 (1.5), Pos = 2.0 (1.6)		Neg = 0.8 (1.2), Pos = 0.8 (1.2)	
Iritis, N = 341, 230*	Neg = 1.8 (1.6), Pos = 2.5 (1.7)	p < 0.001	Neg = 2.2 (1.5), Pos = 2.6 (1.5)	p = .02	Neg = 0.7 (1.2, Pos = 0.9 (1.3)	
Lumbar spine disease, N = 146, 425*	Neg = 0.5 (1.3), Pos = 2.5 (1.6)	p < .0001			Neg =0.3 (1.0), Pos = 0.9 (1.3)	p < .0001
Psoriasis N = 461, 110*	Neg = 2.0 (1.7), Pos = 2.3 (1.6)		Neg = 2.2 (1.5), Pos = 2.6 (1.5)		Neg = 0.8 (1.2), Pos = 0.8 (1.3)	
Sex, N = 125, 466*	F = 1.7 (1.6) M = 2.2 (1.7)	p = 0.0001	F = 2.0 (1.5), M = 2.4 (1.5)	p = 0.003	F = 0.8 (1.3), M = 0.8 (1.2)	

* Number of subjects Neg, Pos.

This can be compared to 11 patients who did not progress over 10 years (and who had initial scores of less than 12 to remove the ceiling effect): 8/11 (72%) were men, the average age was 38 years, age of onset 23 years, iritis was present in 5/11 (45%), and 5/11 (45%) had peripheral involvement; they exercised on average 3 h/week.

To extrapolate to age at first radiological change. Assuming the change in AS is linear, with an average change over any 10 year period of 2.55 points on the BASRI scale (36%), the rate of change is thus 1 point every 4 years. The average BASRI score at time of symptom onset being 5 for an average patient aged 28 (see Table 3), it would then have been an estimated 20 years (i.e., 5 × 4 yrs) before symptom onset that radiological change began (i.e., at 8 yrs of age) (Figure 4).

DISCUSSION

Ours is the first cross sectional and longitudinal study specifically examining radiological outcome in AS in terms of the neck, lumber spine, hips, and SI joints (the peripheral joints and thoracic spine are not included in BASRI). However, there are some aspects of the design of the study

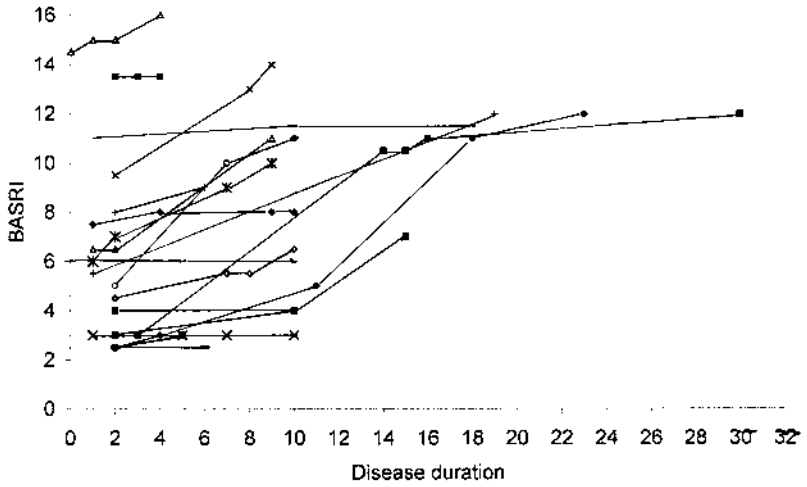

Figure 2. Longitudinal radiographs taken from time of symptom onset plotted against disease duration (n = 20).

Table 4. Radiological progression of a 10 year period.

Disease Duration, yrs	Age at First Assessment, yrs	BASRI, Year 0	BASRI, Year + 10	Change	Percentage Change
0–10 (n = 15)	28.3 (± 10)	5.0 (± 2)	8.0 (± 4)	2.9 (±3)	29
10–20 (n = 20)	35.8 (± 11)	8.2 (± 4)	11.3 (± 3)	3.1 (± 2.5)	40
20–30 (n = 19)	43 (± 5)	9.6 (± 3)	11.4 (± 3)	1.6 (±1)	36
				p = 0.1	p = 0.4

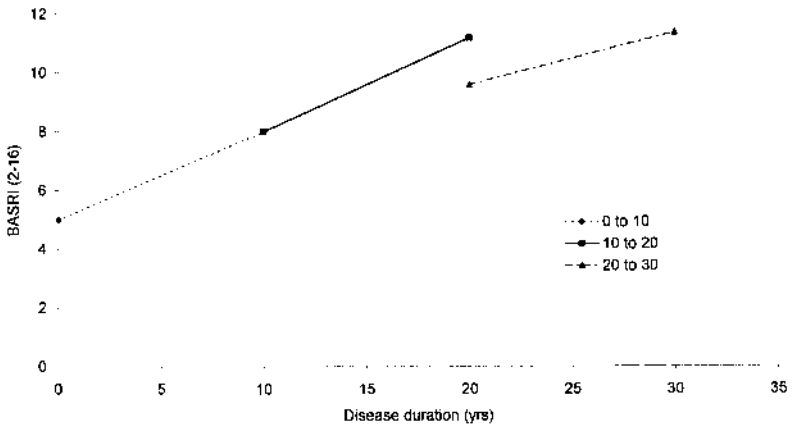

Figure 3. Rate of radiological change over 10 year intervals (n = 53).

that need to be considered. AS is defined as symptomatic sacroiliitis and therefore, by definition, all our patients had sacroiliitis. Conceivably some patients may begin with cervical or thoracic disease and then have descending involvement or may indeed have spinal disease without SI involvement. However, this is almost certainly a rare phenomenon[10,11]. In addition it could be argued that the patients followed longitudinally from time of onset of first symptoms are those who received an early diagnosis and were referred to a tertiary referral center. Thus, these subjects probably represent a severe group with perhaps the most rapidly progressing disease. Yet, even among this population of patients the radiographic progress of the disease appears to be quite slow and gradual.

The clinically significant difference has not been evaluated for BASRI and will need to be examined to establish endpoints for clinical trials and correct interpretation of scores. Hypothetically, it is possible that a one point change

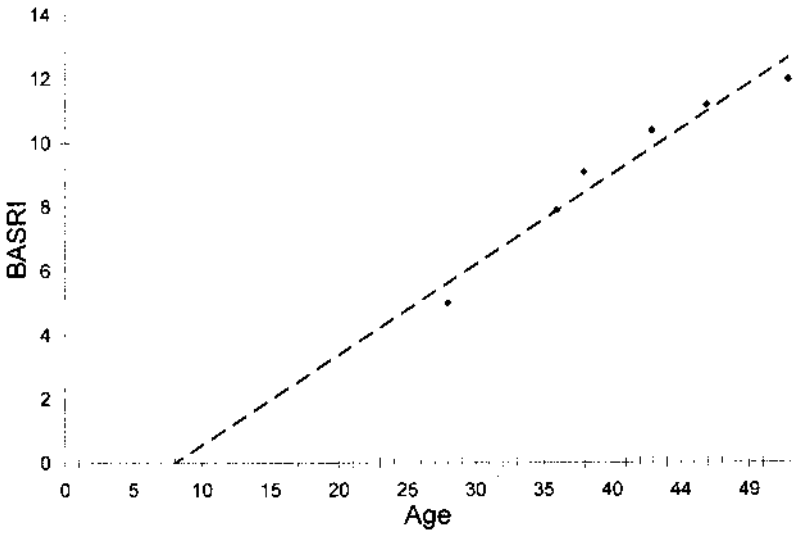

Figure 4. Extrapolation from time of onset of symptoms.

in the neck score would have a greater clinical significance to the patient than a one point change in the SI joint score. However, the change needed for clinical significance in BASRI as a whole has not been investigated.

This study examined a hospital population and showed linear progression of disease. However, the study probably suffers from left censoring and as such it would be expected that the most severe cases are referred to this tertiary center. This would normally imply that there would be differential exclusion of patients with mild disease early in the course of their illness, allowing for their inclusion only later as the disease became more problematic[12]. Thus, patients with inherently milder disease are seen later in their disease course than those with more severe disease. The progression in this case would appear to be rapid at the beginning and slower as disease duration progresses. However, this selection bias does not appear to be observed in the AS population, perhaps therefore lending weight to the argument that AS is a linearly progressive condition. Although it is theoretically possible that the patients who do continue to attend hospital have ongoing symptoms while non-attendees may have "burn out" of disease, there has as yet been no evidence among non-hospital patients that the disease goes into remission[13]. In addition, the extrapolation to age of first radiological change is based on the assumption that rate of change before symptoms (generally SI changes) is equal to change after symptoms (generally spinal change). Only by investigating the rate of SI change will we be able to truly estimate the timing of first radiological damage. This would require magnetic resonance imaging of young individuals who are in the highest risk groups, such as those with a family history, iritis, etc[14].

A previous study has shown that severity of BASRI is associated with disease duration, sex, and hip disease[15]. In terms of time of first radiological change, rate of progression, variation among individuals versus the general AS population, and factors determining this variation, our study shows:

1. In the majority of patients, AS begins in the SI joints and progresses up the spine (the thoracic spine is not evaluated within the BASRI score). Thus, spinal involvement is largely an expression of disease duration. However, the amount of change accounted for by the factors examined was low. It is possible that the majority of the variation in severity of radiological change may be accounted for by genetic factors, as has been suggested for disease activity and functional measures[16]. Iritis appears to be a factor associated with severity. It could be argued that severe disease is simply more widespread disease (i.e., severe cervical involvement is associated with severe lumbar disease) and that iritis is just a reflection that the disease involves more areas of the body. However, bowel disease and psoriasis are not associated with more radiological involvement. Thus, perhaps iritis may be used as a predictor of more radiological change. The level of disease activity (BASDAI) does not appear to influence radiological change. However, disease activity can change daily but BASRI score is only sensitive to change at 2 years. The effect of increased inflammation and disease activity may not be seen in the radiographs until 2 years later. Thus, current BASDAI does not correlate with radiological damage, but disease activity measures of 2 years ago might show a relationship with current radiographs. Serial measurements of disease activity into mean activity estimates may show a better relationship with disease progression.
2. The hips become involved in about 20-30% of individuals and predict a more severe outcome for the cervical spine. Patients with hip disease appear to represent a separate

cohort of AS subjects. It is known that in general they have a younger age at onset[15,17] and have more severe disease radiologically (results from this study suggest this is focused mainly at the neck). In half the people with hip involvement there appears to be early hip disease (i.e., radiological change early in the disease duration of AS). However, in the other half of patients the involvement of the hip may not be used as a predictor of severity of AS, as there is no radiological change in the hip until the AS is established. In 20% of patients disease may move from the SI joints to the cervical spine without involving the lumbar spine. However, with progressing disease duration it appears probable that the lumbar spine will become affected (90% of patients show lumbar involvement after 30 or more years of disease).
3. AS is a linearly progressive condition with about 35% change or an increase of 2.5 on the BASRI (2-16) scale every 10 years. However, individuals show a great deal of variation in rate of progression (Figure 2). A descriptive examination of those progressing the most versus those progressing the least suggests important factors may include variables such as sex and prevalence of iritis. However, a larger study designed specifically to examine variables affecting rate of progression is under way.
4. The rate of change can be extrapolated backwards to estimate the time of first radiological changes to be at about age 8 years.

This study has a retrospective design for reasons of cost and ethical considerations (i.e., taking radiographs of non-affected patients) that has allowed us to examine a greater number of patients using radiography. In addition, all patients who attend the hospital are always given the same questionnaire with the same questions at every visit. Thus, every attempt is made to make the design as close to a prospective method as possible. However, any retrospective study carries some inherent problems (i.e., milder patients may drop out of the system and will not be included). However, a prospective study carried out on 51 Canadian war veterans[18] over a 30 year period examined mobility and spinal restriction (an outcome that can improve with time, as occurred in 27% of the subjects). The study suggests that a predictable pattern of disease emerges in the first 10 years of disease, i.e., severe symptoms in the beginning lead to a severe outcome in the future. This suggestion is supported by findings that oligoarthritis, erythrocyte sedimentation rate > 30 mm/h, sausage-like finger or toe, and limitation of range of motion of lumbar spine (i.e., those with a widespread severe disease) predict a poorer outcome in the future[16]. However, studies on functional and social aspects of AS[19] suggest that although careful followup of patients within the first 10 years of disease is needed, changes still occur after 20 years of disease. Our findings suggest that the advancement of disease in terms of radiological progression occurs in bursts and that individuals show a great deal of variation, some of which may be accounted for by presence of hip disease, iritis, and sex of the patient. Patients with severe disease in the initial 10 years will continue to have progressive and severe disease in the future. The disease progresses in a linear manner at the population level, but for the individual it progresses with a series of bursts of change. Further work with greater numbers of patients may show different subsets of patients (i.e., linear progression, exponential progression, sigmoid progression, no progression) as has been shown to occur in rheumatoid arthritis[9]. Of 48 male patients radiographed in the 30 year prospective study[18], 6 (12.5%) showed SI joint involvement only (with no regional disease). Our cross sectional findings, which included women in the sample, also showed that a maximum of 10% of patients will have SI joint involvement only.

In summary, radiographic progression appears to be constant over the course of AS. With advancing disease duration there is advancing disease, and the involvement of the lumbar spine increases chances that the cervical spine will become affected. Hip disease and iritis separately point to greater radiological cervical change. There is significant variation and spread among patients with AS. However, the disease progresses at an estimated rate of 2.5 points on the BASRI scale or 35% every 10 years. This rate can be used to make a very crude extrapolation to timing of first radiological change, which could be from as young as 8 years. However, the time interval between the "pulling of the trigger" and onset of disease remains unknown.

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