Predictors of Longterm Outcome in Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To determine predictors of longterm outcome in ankylosing spondylitis (AS).

Methods. Data were collected retrospectively on constitutional and environmental factors that may predict outcome in AS in 311 patients (252 men, 81%). Univariate statistics and multivariable linear regression analyses were used to identify factors correlated with disease outcome, which was defined in terms of radiological (Bath AS Radiology Index, BASRI) and functional status (Bath AS Functional Index, BASFI).

Results. Disease duration, sex, and iritis are independently associated with BASRI and account for 23% ($p < 0.001$) of variation in radiological scores (BASRI-t), a measure that includes the hip joint in the score. Radiological hip involvement is significantly associated with higher scores of spinal radiological change (BASRI-s) ($p < 0.001$). Cigarette smoking, radiological status, and Bath AS Disease Activity Index score (BASDAI) are independently associated with and account for 50% of variability in functional status ($p < 0.001$).

Conclusion. Much of the variability in disease severity in AS remains unexplained. All but one of the factors associated with outcome in this study are inherent. This suggests that genetic factors have a greater influence than environmental factors on radiological progression and disability in AS. It may, however, be possible to improve longterm functional outcome in AS by targeting high risk individuals early in the disease course with more aggressive management strategies and encouraging smoking cessation in all patients with AS. (J Rheumatol 2003;30:316–20)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS OUTCOME RADIOLOGY FUNCTION

Ankylosing spondylitis (AS) is a chronic progressive inflammatory disorder affecting the axial skeleton and peripheral joints. This process leads to a variable degree of restricted mobility of the spine with consequent loss of functional capacity. Susceptibility to AS has been shown to be largely genetically determined, and it has been suggested that disease severity is at least partially determined by genetic factors[1]. The relative contribution of genetic and environmental factors to disease severity has not, however, been elucidated.

Investigation of environmental and constitutional risk factors predicting the severity of AS may offer insights into pathogenesis and approaches to disease management. Studies have identified male sex[2], early age at disease onset[3,4], presence of hip arthritis[4], and peripheral oligoarthritis[4-6] as constitutional factors that are correlated with a poorer prognosis in AS. The influence of environmental factors on outcome has also been investigated. Cigarette smoking has been associated with worse clinical, functional, and radiological outcome in AS[7]. Patients with lower education levels[6], in lower socioeconomic groups[8], and those with more physical occupational activities[2] have also been noted to have a poorer prognosis.

Assessment of outcome in AS relies on a number of measures, as few endpoints are clearly defined. Radiological change is an important outcome in AS because it is an objective marker that reflects the cumulative process of destruction over time. The Bath Ankylosing Spondylitis Radiology Index (BASRI) was developed to facilitate the scoring of radiological change in the spine and hips and has been shown to be reliable, specific, and sensitive to disease progression at 2 years[9,10]. However, functional disability may reflect more accurately the effect of the disease on the quality of life of the individual. The functional deficit in AS results from a combination of axial and peripheral joint lesions, pain, and soft tissue inflammation. Functional disability is an important outcome measure in AS that has been shown to predict the economic costs of care of patients[11]. The Bath Ankylosing Spondylitis Functional Index (BASFI) is a validated measure that focuses on 10 questions pertaining to function, measured on a visual analog scale[12].

We sought to determine patient characteristics that might explain the variability in outcome in AS. For this study, outcome was defined using the endpoints of damage and its functional consequences measured by BASRI and BASFI. The factors examined included some that are potentially modifiable along with a number of those inherent to the individuals

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in the study. We also sought to indirectly assess the relative contribution to disease severity of genetically determined and environmental factors.

MATERIALS AND METHODS

Study population. Patients were selected from a database containing information on 458 patients who fulfilled the New York Criteria[13] for diagnosis of AS and attend the Royal National Hospital for Rheumatic Diseases. Study subjects (n = 311) were selected if they had a complete set of radiographs, and if data on the variables of interest were available. We compared the study group (n = 311) to the nonselected group (n = 147) and found that the 2 groups were similar in terms of disease duration at time of study (23.5 vs 20.1 yrs), percentage male (82% vs 79%), and mean age at disease onset (22.9 vs 22.1 yrs). Information regarding predictor variables, including medical diagnosis of peripheral joint involvement, iritis, psoriasis, and inflammatory bowel disease (IBD) and age at disease onset was abstracted retrospectively from patient medical records. Disease duration at time of radiographs was obtained retrospectively from the medical notes, as was time to diagnosis of AS from symptom onset, information regarding cigarette smoking (ever/never), occupation in the early years of disease, marital status at disease onset, positive family history (i.e., affected first-degree relative), highest education level, and anatomic location of first AS symptoms. Data were corroborated using questionnaires completed by the study patients. Data regarding iritis, psoriasis, IBD, family history of AS, hip and peripheral joint involvement, and smoking were recorded over the entire duration of disease (i.e., ever/never). Data regarding marital status, area of first symptom, education level, and occupation were recorded at time of disease onset.

Patients were categorized into socioeconomic groups according to their occupation[14]. In addition, occupation was categorized according to its physical demands into sedentary, active, or manual. The Bath Ankylosing Spondylitis Disease Activity Index score (BASDAI) was completed by all patients in the same year as radiological and functional assessment. Table 1 lists the variables examined in this study.

Outcome measurement. Full sets of radiographs (anteroposterior and lateral lumbar spine, cervical spine, sacroiliac joints, and hip joints) were scored separately, by 2 trained independent readers (MD, SB) using BASRI. The BASRI-total score (BASRI-t) includes radiological change in the spine, sacroiliac, and hip joints (range 2–16), and BASRI-spine (BASRI-s) is a subset of this score that excludes the hip joints (range 2–12)[10]. Two additional trained readers (KM, AC) reviewed cases where discrepancies between scores existed and a consensus was reached. Patients completed functional (BASFI) assessments in the same year as radiological assessment.

Statistical analysis. Statistical analyses were performed individually for each of the 2 outcome measures and for both BASRI-t and BASRI-s. All variables were analyzed using linear regression analysis to identify factors associated with higher BASRI and BASFI scores, indicative of more severe disease. Multivariable linear regression models were constructed using stepwise selection to evaluate the independent association of each variable that was significant in univariate analyses. Final models included only variables with p values < 0.05. SPSS was used for all analyses.

RESULTS

Demographic data and distribution of the variables tested among the 311 patients are shown in Table 1. Of 311 patients in the study, 254 (82%) were male and the average age (± standard deviation) at disease diagnosis was 22.9 ± 8.3 years. BASRI and BASFI scores were normally distributed, with mean BASRI score 9.0 ± 4.1 (range 2–16), mean BASRI-s score 8.22 ± 3.3 (range 2–12), and mean BASFI score 4.79 ± 2.6 (range 0–10).

BASRI. The results of univariate linear regression analyses examining the association between potential predictive factors and radiological status (BASRI-t) showed that disease duration ($p < 0.0001$), male sex ($p = 0.022$), history of iritis ($p < 0.0001$), current marital status ($p = 0.025$), and highest education level attained ($p = 0.034$) were all significantly associated with higher radiological score. Multivariable regression analysis showed that, of these factors, disease duration, male sex, and a history of iritis are independently associated with and together account for 23% ($p < 0.0001$) of the variation in BASRI-t (Table 2). In a separate analysis with spinal radiological change (BASRI-s) as the dependent variable, in which radiological changes in the hip joints are excluded, hip involvement was significantly associated with higher spinal radiological scores ($p < 0.001$). Hip involvement remained independently associated with outcome in a multiple regression model, where radiological hip involvement, longer dis-

Table 1. Characteristics of AS study subjects and demographic data (n=311).

Variable	
Disease duration, mean yrs (SD)	23.5 (11.3), range 1–51
Delay in diagnosis, mean yrs (SD)	7.7 (7.7), range 0–35
Age at onset, mean yrs (SD)	22.9 (8.3), range 5–56
Male sex, n (% total)	254 (82)
History of iritis, n (%)	120 (39)
History of psoriasis, n (%)	69 (22)
History of IBD, n (%)	23 (7)
Hip involvement, n (%)	81 (26)
Peripheral joint involvement, n (%)	130 (42)
Affected family member, n (%)	70 (23)
Ever cigarette smoker, n (%)	120 (39)
Area first symptomatic, n (%)	
Low back	191 (61)
Hip/groin	46 (15)
Knee/ankle	31 (10)
Exercise level (%)*	
1	57 (48)
2	48 (15)
3	101 (32)
4	65 (21)
5	36 (7)
Education level (%)	
< 8 yrs	11/217 (5)
8–12 yrs	108/217 (50)
> 12 yrs	98/217 (45)
Occupational activity level (%)	
Active	66/283 (23)
Sedentary	164/283 (58)
Manual	53/283 (19)
Marital status (%)	
Separated/divorced	20 (6)
Married/widowed	220 (70)
Single	71 (23)
Social status**, n	A=15, B=105, C-74, D=23, E=35, F=59

*1 = None; 2 = < 2 h/week; 3 = 2–4 h/week; 4 = 5–9 h/week; 5 = 10+ h/week.

** A: director; B: professional; C: administrative; D: skilled; E: unskilled; F: farmer

Table 2. Results of multivariable regression, showing the contribution of the significant predictors to the models for each outcome measure.

	Intercept*	CI	p
BASRI	3.4**	1.9–4.8	
Male sex	+ 2.440	1.055–3.825	0.001
Iritis	+ 2.631	0.673–4.590	0.009
Disease duration, yrs	+ 0.146	0.107–0.186	0.0001
BASRI–spine	3.4**	2.266–4.621	
Male sex	+ 1.775	0.622–2.928	0.001
Iritis	+ 1.526	0.27–3.323	0.044
Hip involvement	+ 3.684	1.028–6.341	0.001
Disease duration, yrs	+ 0.110	0.08–0.141	0.0001
BASFI	1.103†	1.99–4.2	
Radiological change, unit increment in BASRI score	+ 0.209	0.144–0.275	0.0001
Disease activity, unit increment in BASDAI score	+ 0.323	0.2–0.415	0.0001
Smoking	+ 0.618	0.0108–1.22	0.02
Smoking and psoriasis together	+ 1.25	0.001–2.56	0.048

*Value corresponds to that of a "baseline person," defined below.
**In this case, the baseline person is female with disease duration = 0 years. For example, the mean BASRI–s score for a woman with disease duration 10 years, with no hip disease or iritis, is 4.5; while the mean BASRI–s for a man with disease duration 10 years with hip disease and iritis is 11.5.
† In this case, the baseline person is male or female.

ease duration, male sex, and history of iritis accounted for 35.5% of variation in BASRI-s ($p < 0.001$) (Table 2).

BASFI. Univariate analyses examining the association between potential predictive factors and current functional status (BASFI) showed that radiological status measured by BASRI in the same year as BASFI, higher disease activity score, history of smoking, peripheral joint involvement, psoriasis, and hip involvement were all associated with higher BASFI scores ($p < 0.0001$ for all factors). Examining these factors in a multivariable analysis with stepwise selection, we found that radiological status, higher disease activity score, and smoking were independently associated with current function ($p < 0.001$) and accounted for 50% of the variation seen in BASFI (Table 2). There was a significant interaction between smoking and psoriasis, such that those patients with psoriasis who smoked had poorer function than either nonsmokers with psoriasis or smokers without psoriasis ($p = 0.001$) (Figure 1).

Patient characteristics not associated with either BASRI or BASFI in univariate or multivariable analyses included many environmental variables such as exercise, occupation related variables, and delay in diagnosis. In addition, several inherent variables including age at onset of AS, site of first AS symptoms, positive family history, and associated IBD were not associated with outcome.

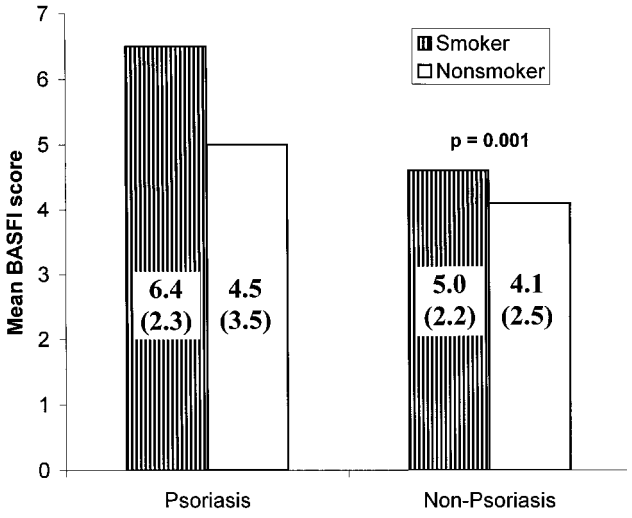

Figure 1. Interaction between cigarette smoking and functional status (BASFI) in patients with psoriasis compared to those without psoriasis ($p = 0.001$). Figures in bars denote mean (SD) BASFI score.

DISCUSSION

Outcome in patients with AS in terms of both function and radiological change can, in part, be predicted by clinical characteristics identifiable early in the disease course. However, the variables examined within this study fail to account for most of the variability in radiological outcome in a hospital based group of patients with AS, as 80% of the variation in BASRI remains unaccounted for. Further, those factors independently associated with worse radiological outcome (disease duration, male sex, iritis, and hip involvement) are constitutional characteristics of the individual. It appears, therefore, that an influence of modifiable factors such as exercise, occupation, and smoking on longterm radiological outcome is not substantiated by our retrospective data.

Modification of functional outcome in AS, which is important to an individual's quality of life and ability to work, may, however, be more feasible. Two of the 3 factors that account for 50% of the variability in functional outcome are potentially modifiable — disease activity score and cigarette smoking. Disease activity score reflects pain, fatigue, stiffness, and discomfort and has been shown to be modifiable with physiotherapy, drug treatments, and pain management techniques[12].

A number of studies have attempted to define clinical factors that may predict disability in AS. A better outcome occurs more frequently in women, a finding with which our results concur[2]. This study also supports the finding of other studies that hip involvement predicts a worse outcome, in terms of both radiology and function[2,4,9,15]. In contrast to previous studies, we did not find an association between peripheral oligoarthritis and more severe outcome[4-6]. There has been conflicting evidence about the importance of age of onset as a predictor of disease severity, with 2 studies finding an association[3,4] and another failing to do so[2]. Age at onset was not significantly associated with either outcome in this study. Our finding that delay in disease diagnosis does not affect outcome corroborates previous reports[5,6] that failed to establish that early diagnosis in itself improves functional outcome. This association may, however, be difficult to detect because individuals with milder symptoms and disease may tend to be diagnosed later.

The finding of a correlation between secondary diseases and disability in AS concurs with evidence that iritis is associated with poor outcome[6]. Our findings contrast with another study that found that psoriasis and IBD were associated with worse disease outcome in AS[16].

Cigarette smoking has been associated with worse clinical, functional, and radiological outcome in AS. We substantiate the evidence of an association between cigarette smoking and poor functional outcome in AS[7]. Smoking has also been shown to have an influence on the disease course in psoriasis[17]. It is interesting, therefore, to note the interaction we found between smoking and psoriasis, such that smoking is associated with worse functional scores in AS patients with psoriasis. It is possible that smoking increases the severity of psoriasis, which in turn is associated with increased AS disease activity.

Occupational and socioeconomic factors and their influence on disability in AS have also previously been examined[2,8]. Findings from these studies that patients with lower socioeconomic status and lower education levels and those with more physically demanding occupations have a poorer prognosis were not replicated in this study.

In this study, we corroborate findings that selected environmental factors play little role in determining disease severity in AS[18]. It is therefore likely that genetic factors and hormonal influences (as suggested by the predictive value of male sex) have a greater influence on outcome in AS. More specific identification of the method of inheritance of disease severity and the role of genetic factors in prognosis will require further investigation.

Limitations of this study include the fact that it is based in a tertiary referral center and patients with more severe AS may be overrepresented. These results may, therefore, not be generalizable to all patients with AS in the community, and it is possible that environmental variables such as occupation and exercise could have important effects in subjects with milder disease. In addition, recall bias may be present in the data obtained from the questionnaires. We did, however, attempt to minimize this bias by validation of the patient-generated data by reference to documentation in the patient hospital records. Additionally, cross sectional analyses are limited by difficulties in separating cause from effect and, in turn, accounting for whether subjects may change their behaviors in response to concerns about disease development. Severe AS may lead to depression and unemployment, which could increase cigarette consumption. The finding that higher education level is associated with less severe disease may reflect less disruption to the lives of subjects with mild disease than those with severe arthritis, who are thus able to continue their education for longer. Alternatively, an education beyond school-leaving level may allow patients to manage their disease better. Due to the variation in disease duration at time of radiographs, the information on some individuals may be incomplete, and thus right censorship may occur. However, as the mean disease duration was relatively long (23.5 yrs), this is unlikely to have greatly affected our results.

Outcome for individuals with AS is variable and difficult to predict early in the disease course. Despite consideration of many variables with potential effect on outcome in this study, some 80% of the variation in radiological status and 50% of the variation in functional status remain unaccounted for. It is likely that AS severity is largely controlled by genetic factors. However, encouraging patients not to smoke may help to preserve function in AS. Further, male sex, iritis, hip involvement, and higher disease activity scores appear to portend a worse prognosis in AS. Thus, targeting of individuals with these risk factors early in the disease course with more aggressive therapies may improve functional outcome and quality of life for these patients.

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