Determinants of Early Radiographic Progression in Ankylosing Spondylitis

PAMIR ATAGUNDUZ, SIBEL ZEHRA AYDIN, CENGIZ BAHADIR, BURAK ERER, and HANER DIRESKENELI

ABSTRACT. ***Objective.*** To investigate the demographic and clinical characteristics associated with early, extensive radiographic changes in ankylosing spondylitis (AS).

Methods. Radiographic severity was assessed cross-sectionally in 235 patients with AS using the Bath AS Radiological Index spine score (BASRI-s). Patients with extensive radiographic changes on the lumbar portion of BASRI-s were defined as the early axial ankylosis (EAA) Group. ANCOVA and logistic regression analyses were used to identify factors affecting EAA.

Results. Most study patients were men (139/235, 59.0%). Mean disease duration was 12.4 ± 9.3 years. Fifteen percent of women and 34.8% of men with AS were in the EAA group. HLA-B27-positive men with AS had significantly higher BASRI-lumbar scores, while HLA-B27 had no effect on radiographic progression of axial disease in women with AS. Peripheral joint involvement was associated with slow radiographic progression. Hip involvement had no effect on axial progression but uveitis was more frequent in the male EAA group. The odds for an HLA-B27-positive male patient with AS who did not have peripheral arthritis of having a BASRI-lumbar score of 3 or higher were 3.4 (77% chance to have axially progressive disease). Presence of uveitis increased these odds to 93%. Only 15% of female patients with AS had EAA, and the absence of peripheral arthritis was the only clinical measure associated with EAA in this group.

Conclusion. EAA was more frequent in men with AS than in women. Absence of peripheral arthritis, HLA-B27 positivity, and uveitis were associated with multiple syndesmophytes or fusion of multiple vertebrae of the lumbar vertebrae. (First Release Sept 15 2010; J Rheumatol 2010;37:2356–61; doi:10.3899/jrheum.100094)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS RADIOGRAPHIC PROGRESSION GENDER SEVERITY

Ankylosing spondylitis (AS) is a longstanding, chronic inflammatory disease with a relatively slow rate of progression. Future restriction of spinal mobility is the major concern of patients with AS at the time of diagnosis; about 40% of patients have severe functional loss several decades after the onset[1,2,3,4]. The rate of radiographic progression differs substantially among patients with similar durations of AS[2,5,6]. At present, knowledge about prognostic factors affecting radiographic severity for individual patients is sparse. Previously, peripheral arthritis has been suggested to be a predictor of disease progression[1] and loss of function[7,8]. Similarly, male sex, uveitis, and hip involvement were found to be associated with radiographically progressive axial disease[9,10,11,12,13,14]. However, several studies assessing the role of HLA-B27 on radiographic severity reported no association with progression[13,15,16].

Previous data on the natural course of AS suggest that up to 15% of patients have an accelerated disease course within the first decade after disease onset. This accelerated functional loss seems to predict the disease severity in longstanding AS[1].

We therefore aimed to determine the association of demographic and clinical characteristics affecting disease severity in patients with AS with short disease duration. We used the Bath Ankylosing Spondylitis Radiology Index for the spine (BASRI-s) to determine the severity[17].

MATERIALS AND METHODS

Patients and data collection. Three hundred sixty-nine consecutive patients with AS diagnosed according to the modified New York criteria at 4 different medical centers in Istanbul, Turkey, were registered between January 2003 and September 2010 for a prospective followup after a final evaluation at the Marmara University Hospital Rheumatology outpatient clinic[18]. At each medical center, patients completed questionnaires on personal and medical history and underwent clinical evaluation by an experienced physician. Patients meeting the modified New York criteria were then referred to the rheumatology department of Marmara Medical School. Final enrollment in the study was done by 2 rheumatologists. Patients with a history or

From the Department of Rheumatology, Marmara University Faculty of Medicine; Haydarpasa Numune Training and Research Hospital; and Department of Rheumatology, Istanbul University Faculty of Medicine, Istanbul, Turkey.

P. Atagunduz, MD, Associate Professor; S.Z. Aydin, MD, Rheumatology Fellow; H. Direskeneli, MD, Professor, Marmara University Faculty of Medicine, Rheumatology; C. Bahadir, MD, Specialist, Haydarpasa Numune Training and Research Hospital; B. Erer, MD, Assistant Professor, Istanbul University Faculty of Medicine, Rheumatology.

Address correspondence to P. Atagunduz, Marmara University, School of Medicine, Department of Rheumatology, Tophanelioglu Cad. 13/15, Uskudar, Istanbul, Turkey. E-mail: pamiratagunduz@yahoo.com

Accepted for publication July 12, 2010.

current diagnosis of inflammatory bowel disease or psoriasis were excluded.

Clinical and laboratory variables. Clinical and demographic data on age at onset, sex, HLA-B27 status, delay in diagnosis, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels at the time of diagnosis were collected. Data were also collected on family history for AS, uveitis, and hip or peripheral joint involvement along axial disease. Disease duration was defined as the time in years starting from the first low back pain episode until the radiographic analysis.

Radiographs of pelvis, lumbar spine on anteroposterior and lateral planes, and cervical spine on lateral plane were scored using the Bath Ankylosing Spondylitis Radiology Index for the spine (BASRI-s) to determine radiographic severity[17]. BASRI-s is a reliable and valid measure of radiographic damage in AS[19,20]. BASRI-s is based on scoring of the lateral view of the cervical spine (C1 to C7), and the frontal or lateral views of the lumbar spine (Th12 to S1) and the sacroiliac joints. Grading is done as follows: Grade 0: normal findings; Grade 1: dubious changes; Grade 2: slight changes, including erosion, vertebral squaring or sclerosis, with or without syndesmophytes, on fewer than 2 vertebrae; Grade 3: syndesmophytes on more than 3 vertebrae, with or without fusion involving 2 vertebrae; Grade 4: fusion involving more than 3 vertebrae.

Radiographs were scored by a single rheumatologist. The intrareader reliability of the BASRI-s, based on 2 readings of the radiographs of 100 patients performed at least 3 months apart, was 0.975 (95% CI 0.979–0.989).

HLA-B27 was determined by standard microcytotoxicity assays, and whenever the first test result was negative it was repeated to minimize the possibility of an erroneous negative result. Scoring of radiographs of the lumbar vertebral column on anteroposterior and lateral planes was used to investigate the effect of clinical and laboratory factors on early axial progression. Scoring of the radiographs of sacroiliac joints and cervical vertebral column was omitted from the evaluation and BASRI-s score for the lumbar portion was used for statistical analysis.

The University of Marmara institutional review board approved our study, and study patients gave informed consent.

Statistical analysis. Descriptive statistics were used for the data by the calculation of means with SD and range for continuous data. For dichotomous and ordinal data, frequencies were calculated. Differences between the groups were tested by computing OR and 95% CI. Associated p values for dichotomous data were calculated by chi-squared statistics, and p values for continuous data were calculated by Mann-Whitney U tests. Since radiographic progression appears to be a function of time, ANCOVA was used to explore the effect of individual variables on radiographic progression between groups.

The effect of multiple variables [sex, age at onset, disease duration, HLA-B27, hip arthritis (BASRI-hip score ≥ 2), peripheral arthritis, enthesitis, or uveitis] on severe axial radiographic damage was assessed with logistic regression analysis. Interactions between the sets of variables were explored in additional analyses that included the main effect variables and the interaction term for each interaction studied. The exponents of the estimates of those logistic regression analyses were used to calculate OR for each category of radiographic damage. All analyses were performed in SPSS 13.0.

RESULTS

Patients. Three hundred sixty-five patients were registered for followup between January 2003 and September 2010. At the time of analysis, 102 patients were receiving anti-tumor necrosis factor-α therapy, and radiographs of 28 patients were not suitable for evaluation. These patients were excluded from the study and the final analysis was done on 235 patients. All patients fulfilled the modified New York criteria for AS. Demographic features of the study patients and disease characteristics are given in Table 1. Mean age of study patients was 39.1 ± 11.2 years and mean disease duration since the onset of low back pain was 12.4 ± 9.3 years. Most study patients were men (139/235, 59.1%) and 70.2% were HLA-B27-positive (men AS = 75.5%, women AS = 63.3%).

Characteristics of patients according to radiographic progression. Comparison of clinical characteristics and demographic data of patients on the basis of radiographic progression is given in Tables 1 and 2. Sixty-two patients (26.4%) had radiographic evidence of extensive lumbar spine involvement (with a BASRI-lumbar score of Grade 3 or 4). One hundred seventy-three patients (73.6%) had no or early changes of lumbar spine involvement (BASRI-lumbar score of Grade 0, 1, or 2). A history of peripheral arthritis was recorded in 99 (42.1%) patients, enthesitis in 119 (50.6%), hip involvement in 120 (51%), and uveitis by patient report in 55 patients (23.4%). Radiographic change of progression of the lumbar spine was more common in men (mean BASRI-lumbar in male vs female patients: 1.77 ± 0.11 vs 0.97 ± 0.14, respectively; $p < 0.0001$, 95% CI –1.16 to –0.39; Table 3).

As shown, disease duration is associated with radiographic progression[15]. Therefore, univariate ANOVA was used to eliminate the effect of disease duration on radiographic progression. This approach revealed that radiographic progression in the lumbar spine was more extensive in HLA-B27-positive patients with AS (mean BASRI-lumbar in HLA-B27-positive vs negative patients with AS: 1.58 ± 0.12 vs 0.85 ± 0.18, respectively; $p = 0.002$, 95% CI –1.14 to –0.18; Table 3). Disease duration was comparable in HLA-B27-positive and negative patients with AS of both sexes. But when analyzed within gender groups, radiographic progression of axial disease was not affected by the presence of HLA-B27 in women with AS (mean disease duration in HLA-B27-positive vs negative patients with AS 12.24 ± 9.44 vs 12.20 ± 8.80 years; $p = 0.97$, 95% CI –2.45 to 2.55; mean BASRI-lumbar score in HLA-B27-positive vs negative women with AS 1.10 ± 0.18 vs 0.90 ± 0.20; $p = 0.47$, 95% CI –0.81 to 0.36).

HLA-B27-positive men with AS were 3.37 times more likely than HLA-B27-negative men with AS to have an early radiographic progression (mean BASRI-lumbar in HLA-B27-positive vs negative men with AS 1.83 ± 0.16 vs 0.81 ± 0.32, respectively; $p = 0.006$, 95% CI –0.62 to 0.45; Tables 3 and 4).

Radiographic progression of axial involvement was milder in patients with AS who had peripheral joint involvement (mean BASRI-lumbar score in women with AS who had peripheral arthritis vs women who did not have peripheral arthritis 0.68 ± 0.16 vs 1.30 ± 0.16, respectively; $p = 0.011$, 95% CI 0.27 to 1.07; mean BASRI-lumbar score in men with AS who had peripheral arthritis vs men who did

Table 1. Demographic and clinical features of study patients with AS.

Features	Whole Group	Women	Men	p
No. (%)	235 (100)	96 (41)	139 (59)	
Mean age, yrs, ± SD	39.1 ± 11.2	41.8 ± 11.4	37.2 ± 10.7	0.75
Mean age at onset, yrs, ± SD	27.1 ± 9.8	29.7 ± 10.2	25.1 ± 9.0	0.87
Mean disease duration, yrs, ± SD	12.4 ± 9.3	12.14 ± 9.0	12.14 ± 9.5	0.94
Delay in diagnosis, yrs, ± SD	6.7 ± 7.4	7.4 ± 7.9	6.2 ± 7.1	0.78
HLA-B27, %	70.2	63.3	75.5	0.05
Peripheral arthritis, %	42.1	53.3	30.9	0.001
Enthesitis, %	50.6	64.8	36.4	0.001
Hip involvement, %	51.0	52.0	50.0	0.65
Uveitis, %	23.4	26.2	20.6	0.09
Early axial ankylosing, %	26.4	15.0	34.8	0.001

Table 2. Demographic and clinical features of AS patients according to radiographic progression.

Features	Slow Progression	Rapid Progression	p
No. women/men	85/88	15/47	0.001
Mean age, yrs, ± SD	37.5 ± 11.0	44.0 ± 9.4	0.07
Mean age at onset, yrs, ± SD	27.2 ± 9.7	27.5 ± 9.9	0.36
Mean disease duration, yrs, ± SD	10.6 ± 8.5	12.8 ± 8.7	0.09
Delay in diagnosis, yrs, ± SD	6.4 ± 7.1	7.8 ± 7.1	0.08
HLA-B27, %	63	86	0.005
Peripheral arthritis, %	47	21	0.001
Enthesitis, %	54	24	0.001
Hip involvement, %	53	46	0.35
Uveitis, %	20	28	0.26

Table 3. Factors associated with axial ankylosis in patients with AS.

Variables	Mean BASRI-lumbar Score					
	Whole Group	p	Men with AS	p	Women with AS	p
Women	0.97 ± 0.14		—		0.97 ± 0.14	
Men	1.77 ± 0.11	< 0.0001	1.77 ± 0.11		—	
HLA-B27-positive	1.58 ± 0.12		1.83 ± 0.16		1.10 ± 0.18	
HLA-B27-negative	0.85 ± 0.18	0.002	0.81 ± 0.32	0.006	0.90 ± 0.20	0.47
Peripheral arthritis						
Present	0.93 ± 0.14		1.21 ± 0.22		0.68 ± 0.16	
Absent	1.78 ± 0.11	< 0.0001	2.04 ± 0.15	0.003	1.30 ± 0.16	0.011
Enthesitis						
Present	1.02 ± 0.18		1.42 ± 0.30		0.74 ± 0.19	
Absent	1.72 ± 0.17	0.007	1.98 ± 0.21	0.13	0.98 ± 0.26	0.47
Uveitis						
Present	1.57 ± 0.21		2.21 ± 0.33		1.00 ± 0.25	
Absent	1.41 ± 0.11	0.53	1.68 ± 0.15	0.15	1.00 ± 0.15	0.96
Hip involvement						
Present	1.36 ± 0.13		1.60 ± 0.19		1.00 ± 0.16	
Absent	1.55 ± 0.13	0.33	1.96 ± 0.18	0.18	0.93 ± 0.18	0.65

not have peripheral arthritis 1.21 ± 0.22 vs 2.04 ± 0.15; p = 0.003, 95% CI 0.09 to 0.91; Table 3). Family history for AS had no effect on axial radiographic changes (mean BASRI-lumbar score in patients with family history vs those without family history 1.49 ± 1.45 vs 1.50 ± 1.48; p = 0.85, 95% CI –0.58 to 0.49). Mean delay in diagnosis was 6.13 ± 6.2 years and it did not differ between the sexes (mean delay in diagnosis in women vs men with AS 6.11 ± 6.05 vs 6.11 ± 38 years; p = 0.99, 95% CI –2.01 to 2.00).

A history of enthesitis was protective for lumbar extension of the disease in the whole group, but when analyzed within gender groups the protective effect was lost (Table 3). A history of uveitis was associated with extensive radiographic progression in male patients only. Radiographic pro-

Table 4. Logistic regression analysis of early axial ankylosis.

Characteristic	ß Estimate	SE	p	95% CI
Estimate in patients with AS*				
Sex	0.79	0.41	0.05	1.10–4.90
HLA-B27	1.05	0.50	0.03	1.06–7.76
Absence of peripheral arthritis	1.16	0.42	0.007	0.13–0.72
Uveitis	0.67	0.42	0.11	0.85–4.49
Hip involvement	–0.34	0.38	0.37	0.33–1.50
Constant	–1.47	0.27	< 0.0001	
In men with AS**				
HLA-B27	1.69	0.80	0.03	1.12–26.71
Absence of peripheral arthritis	1.01	0.53	0.05	0.12–0.90
Uveitis	1.04	0.54	0.05	1.02–8.32
Hip involvement	–0.20	0.47	0.96	0.38–0.50
Constant	–1.16	0.43	0.005	
In women with AS***				
HLA-B27	0.63	0.71	0.37	0.46–7.55
Absence of peripheral arthritis	1.42	0.76	0.05	0.05–1.02
Uveitis	0.28	0.73	0.70	0.31–3.60
Hip involvement	–0.91	0.70	0.19	0.10–1.58
Constant	–1.94	0.40	< 0.0001	

* Overall predictive value is 77.4%. ** Overall predictive value is 71.4%. *** Overall predictive value is 84.4%.

gression in the lumbar portion of the vertebral column was not different in patients with and those without hip involvement (mean BASRI-lumbar in patients with vs without hip involvement 1.36 ± 0.13 vs 1.55 ± 0.13; p = 0.33, 95% CI –0.29 to 0.51).

It has been shown that radiographic progression in AS is more severe in men, and that it is a function of disease duration[2]. Therefore, we applied logistic regression models separately for men and women when analyzing the effect of multiple clinical and laboratory measurements on severe radiographic progression (Table 4).

HLA-B27-positive men with AS who have uveitis and no history of peripheral arthritis were 13.0 times more likely to have extensive radiographic progression (OR $e^{(-1.16 + 1.69 + 1.04 + 1.01)} = 2.71^{(-1.16 + 1.69 + 1.04 + 1.01)} = 2.71^{(2.58)} = 13.0$; Table 4).

Among the women patients, a Grade 3 or 4 BASRI-lumbar score was seen in only 15% and women with AS had only a 37% chance to have radiographic changes of early axial progression (Table 1). Absence of peripheral arthritis was the only clinical feature associated with a worse radiographic outcome in women with AS (Table 4).

The mean BASRI-lumbar scores of patients treated with biologic agents did not differ from those treated with conventional disease-modifying antirheumatic drugs (1.37 ± 1.13 vs 1.41 ± 1.01, respectively; p = 0.76, 95% CI –0.91 to 1.21). Disease duration and HLA-B27 prevalence did not differ between these groups.

DISCUSSION

Prognostic information about the future course of AS is helpful for consulting patients and can be used to select patients most at risk for developing severe radiographic damage and hence functional loss. At present, knowledge about accurate prognostic information for individual patients is poorly defined. It was suggested that the rate of natural radiographic progression in patients with AS is rather linear[2,6] and a predictable disease pattern emerges within the first 10 years after the onset of low back pain[1]. In a longitudinal prospective study, Carette, *et al* reported that 74% of patients with mild spinal restriction within the first 10 years did not progress to a more severe category of functional loss after a mean disease duration of 38 years.

We aimed to evaluate the rate of axial radiographic progression in patients with AS who had relatively short disease duration. After a mean disease duration of 12 years, 52.3% of the patients studied had no axial radiographic changes. However, extensive radiographic changes of the lumbar vertebral column were already present in 26.4%, suggesting that a substantial proportion of patients are at risk for developing extensive axial ankylosis and may have severe functional restriction eventually.

In our study, a small set of clinical variables and HLA-B27 testing differentiated patients with extensive axial progression. Radiographic progression was more severe in men with AS and this finding is in accord with previous studies[9,12,21,22]. Disease onset was earlier in male patients, but disease duration did not differ with sex, and age at disease onset did not differ in the more progressive group, as supported by previous studies[2,9]. Interestingly, HLA-B27 was more frequent in the male AS group, and still its overall prevalence of 70.2% was much lower than previously reported[23]. In contrast to previous reports addressing the role of HLA-B27 in disease severity[24,25] and radiographic

progression[26], HLA-B27 was found to be associated with severe radiographic progression in men. However, other studies either did not assess radiographic changes as an outcome measure or had different sets of patients with longer mean disease durations and high HLA-B27 prevalences. The association of HLA-B27 presence with the progression of ankylosis in AS is difficult to address in cohorts where the prevalence of HLA-B27 is as high as 90%. To overcome this difficulty, family studies and studies in siblings were undertaken, and a possible contribution of HLA-B27 was supported by the presence of high heritability of radiographic severity and concordance among siblings[27,28]. In contrast with reports from Europe and North America, our patient group had a lower HLA-B27 prevalence. Interestingly, this low prevalence is in accord with a previous report from the same region[29].

One other difficulty of defining radiographic disease progression toward the vertebral column may be the use of total BASRI-lumbar score, which is the sum of scores of 3 different levels of the vertebral column. Extensive involvement of the sacroiliac joints, increasing the total score, may blunt the limited differences in the total score detected by plain radiographs. As shown, the best predictor for future ankylosis is the presence of syndesmophytes or ankylosis of the vertebral column itself at the time of analysis[30]. We therefore used only the BASRI score of the lumbar portion of the vertebral column[31]. This approach allowed us to choose patients with the highest risk of progression according to current knowledge in the AS literature.

Clinical and genetic factors contributing to early radiographic progression differed between the sexes. This finding was in accord with previous reports[2,9,11,13]. In contrast to previous studies, HLA-B27 was found to be associated with early axial progression in men only. The absence of peripheral arthritis or patient-reported history of uveitis was also associated with multiple syndesmophytes or fusion of multiple vertebrae.

In our patient population, almost 53% of patients with AS had no radiographic changes of the vertebral column except sacroiliitis. Studies addressing radiographic severity in patient groups with almost twice the disease duration are in accord with this slow progression rate[15]. A man with AS who was HLA-B27-positive and without a history of peripheral arthritis was 3.37 times more likely to have axially progressive disease (77% chance to have an axially progressive disease). Adding uveitis to the model when present increased the OR to 13.0 (93% chance to have an axially progressive disease). In contrast, axial progression in women with AS was associated only with the absence of a cumulative history of peripheral arthritis.

A limitation of our data was their cross-sectional nature, and variables shown to be associated with spinal changes may not be "prognostic" factors. On the other hand, median disease duration of 10 years and the strict criteria to discriminate axial progression of ankylosis in the presence of previous research reporting the prognostic value of severity in the first 10 years on future functional loss, one can assume that clinical and genetic factors reported here suggest the presence of possible prognostic factors. To assess the prognostic value of the measures reported here, further studies, prospective in design, are needed.

REFERENCES

1. Carette S, Graham D, Little H, Rubenstein J, Rosen P. The natural disease course of ankylosing spondylitis. Arthritis Rheum 1983;26:186-90.
2. Brophy S, Mackay K, Al-Saidi A, Taylor G, Calin A. The natural history of ankylosing spondylitis as defined by radiological progression. J Rheumatol 2002;29:1236-43.
3. Braun J, Pincus T. Mortality, course of disease and prognosis of patients with ankylosing spondylitis. Clin Exp Rheumatol 2002;6 Suppl 28:S16-22.
4. Brophy S, Calin A. Ankylosing spondylitis: interaction between genes, joints, age at onset, and disease expression. J Rheumatol 2001;28:2283-8.
5. Calin A, Elswood J. The relationship between pelvic, spinal and hip involvement in ankylosing spondylitis — one disease process or several? Br J Rheumatol 1988;27:393-5.
6. Baraliakos X, Listing J, von der Recke A, Braun J. The natural course of radiographic progression in ankylosing spondylitis — evidence for major individual variations in a large proportion of patients. J Rheumatol 2009;36:997-1002.
7. Gran JT, Skomsvoll JF. The outcome of ankylosing spondylitis: a study of 100 patients. Br J Rheumatol 1997;36:766-71.
8. Baek HJ, Shin KC, Lee YJ, Kang SW, Lee EB, Yoo CD, et al. Clinical features of adult-onset ankylosing spondylitis in Korean patients: patients with peripheral joint disease (PJD) have less severe spinal disease course than those without PJD. Rheumatology 2004;43:1526-31.
9. Doran MF, Brophy S, MacKay K, Taylor G, Calin A. Predictors of longterm outcome in ankylosing spondylitis. J Rheumatol 2003;30:316-20.
10. Kidd B, Mullee M, Frank A, Cawley M. Disease expression of ankylosing spondylitis in males and females. J Rheumatol 1988;15:1407-9.
11. Will R, Edmunds L, Elswood J, Calin A. Is there sexual inequality in ankylosing spondylitis? A study of 498 women and 1202 men. J Rheumatol 1990;17:1649-52.
12. Sampaio-Barros PD, Bertolo MB, Kraemer MH, Neto JF, Samara AM. Primary ankylosing spondylitis: patterns of disease in a Brazilian population of 147 patients. J Rheumatol 2001;28:560-5.
13. Lee W, Reveille JD, Davis JC Jr, Learch TJ, Ward MM, Weisman MH. Are there gender differences in severity of ankylosing spondylitis? Results from the PSOAS cohort. Ann Rheum Dis 2007;66:633-8.
14. Mau W, Zeidler H, Mau R, Majewski A, Freyschmidt J, Stangel W, et al. Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year followup. J Rheumatol 1988;15:1109-14.
15. Boonen A, vander Cruyssen B, de Vlam K, Steinfeld S, Ribbens C, Lenaerts J, et al. Spinal radiographic changes in ankylosing spondylitis: association with clinical characteristics and functional outcome. J Rheumatol 2009;36:1249-55.
16. Rudwaleit M, Haibel H, Baraliakos X, Listing J, Märker-Hermann E, Zeidler H, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum 2009;60:717-27.

17. MacKay K, Mack C, Brophy S, Calin A. The Bath Ankylosing Spondylitis Radiology Index (BASRI): a new, validated approach to disease assessment. Arthritis Rheum 1998;41:2263-70.
18. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
19. Wanders AJ, Landewe RB, Spoorenberg A, Dougados M, van der Linden S, Mielants H, et al. What is the most appropriate radiologic scoring method for ankylosing spondylitis? A comparison of the available methods based on the Outcome Measures in Rheumatology Clinical Trials filter. Arthritis Rheum 2004;50:2622-32.
20. Salaffi F, Carotti M, Garofalo G, Giuseppetti GM, Grassi W. Radiological scoring methods for ankylosing spondylitis: a comparison between the Bath Ankylosing Spondylitis Radiology Index and the modified Stoke Ankylosing Spondylitis Spine Score. Clin Exp Rheumatol 2007;25:67-74.
21. Calin A, Mackay K, Santos H, Brophy S. A new dimension to outcome: application of the Bath Ankylosing Spondylitis Radiology Index. J Rheumatol 1999;26:988-92.
22. Spencer DG, Park WM, Dick HM, Papazoglou SN, Buchanan WW. Radiological manifestations in 200 patients with ankylosing spondylitis: correlation with clinical features and HLA B27. J Rheumatol 1979;6:305-15.
23. Schlosstein L, Terasaki PI, Bluestone R, Pearson CM. High association of an HL-A antigen, W27, with ankylosing spondylitis. N Engl J Med 1973;288:704-6.
24. Khan MA, Kushner I, Braun WE, Zachary AA, Steinberg AG. HLA-B27 homozygosity in ankylosing spondylitis: relationship to risk and severity. Tissue Antigens 1978;11:434-8.
25. Spencer DG, Hick HM, Dick WC. Ankylosing spondylitis — the role of HLA-B27 homozygosity. Tissue Antigens 1979;14:379-84.
26. Ward MM, Hendrey MR, Malley JD, Learch TJ, Davis JC Jr, Reveille JD, et al. Clinical and immunogenetic prognostic factors for radiographic severity in ankylosing spondylitis. Arthritis Rheum 2009;61:859-66.
27. Calin A, Elswood J. Relative role of genetic and environmental factors in disease expression: sib pair analysis in ankylosing spondylitis. Arthritis Rheum 1989;32:77-81.
28. Brophy S, Hickey S, Menon A, Taylor G, Bradbury L, Hamersma J, et al. Concordance of disease severity among family members with ankylosing spondylitis? J Rheumatol 2004;31:1775-8.
29. Gunal EK, Sarvan FO, Kamali S, Gul A, Inanc M, Carin M, et al. Low frequency of HLA-B27 in ankylosing spondylitis patients from Turkey. Joint Bone Spine 2008;75:299-302.
30. Baraliakos X, Listing J, Rudwaleit M, Haibel H, Brandt J, Sieper J, et al. Progression of radiographic damage in patients with ankylosing spondylitis: defining the central role of syndesmophytes. Ann Rheum Dis 2007;66:910-5.
31. Liao ZP, Wang QC, Xie QP, Tian MB. [Clinical staging of ankylosing spondylitis]. Nan Fang Yi Ke Da Xue Xue Bao 2006;26:1176-8.