

EXTENDED REPORT

Are there gender differences in severity of ankylosing spondylitis? Results from the PSOAS cohort

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Objective: To examine the clinical and radiographic features in men and women in the Prospective Study of Outcomes in Ankylosing Spondylitis cohort, a large well-defined cross-sectional study of patients with AS, in order to understand the influence of gender in determining the severity of ankylosing spondylitis.

Methods: Extensive clinical assessments and spine radiographs were performed in 302 men and 100 women with AS of ≥ 20 years duration. Radiographs were scored using the Bath Ankylosing Spondylitis Radiographic Index Spine (BASRI-spine) score (range 2–12). Functional impairment was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S).

Results: Radiographic severity was worse among men. The unadjusted median BASRI-spine score for men was 10, compared with 6.5 for women ($p < 0.001$). Functional disability, as measured by the BASFI and HAQ-S, was not different between men and women. However, after adjusting for radiographic spinal damage, women were found to report worse functioning than men at any given level of radiographic damage. Women had a slightly earlier age of disease onset; however, disease duration was identical in both groups. Women more frequently reported family histories of AS in first-degree relatives and were more likely to be treated with intra-articular steroids, sulphasalazine and prednisone.

Conclusions: Among patients with longstanding AS, men have more severe radiographic changes; findings of treatment differences suggest that women may have more peripheral arthritis. At any given level of radiographic damage, self-reported functional limitations were worse for women.

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disorder of joints and entheses that can cause important functional disability and ultimately result in axial fusion in many patients. Historically, AS was always considered to be a disease that overwhelmingly affected men, but recent studies have shown that a significant proportion of patients with AS are women, with the ratio of men to women approaching 2–3:1.^{1–8} Moreover, the severity of disease among women with AS is increasingly being recognised as a cause of significant limitations.⁹ The oft-quoted delay in diagnosis of AS may be, in large part, due to the lack of recognition of the presence of this disease in women.

To better understand the potential influence of gender in determining the severity of AS, we felt it was necessary to better characterise the gender differences in this disease. We compared clinical features, radiographic scores and functional outcomes between men and women in the Prospective Study of Outcomes in Ankylosing Spondylitis (PSOAS) cohort, a study of patients with AS of >20 years disease duration. We also conducted a literature review of studies that have previously compared clinical and radiographic differences between men and women with AS. The patients described here are an extensively characterised cohort of subjects with AS from the modern era, and the findings presented suggest that women with AS have unique features that may affect timely diagnosis, choices of treatment and potentially produce disparities in outcome.

PATIENTS AND METHODS

Patients

Patients were recruited for the cross-sectional component of the PSOAS cohort from Cedars-Sinai Medical Center, Los Angeles, California; Stanford University, Palo Alto, California; the National Institutes of Health, Bethesda, Maryland; the

University of Texas Medical School at Houston, Houston, Texas; and the University of California, San Francisco, California. Inclusion criteria were: meeting the modified New York criteria for AS¹⁰; having AS for ≥ 20 years, dated from the time of onset of persistent inflammatory low back pain or restricted spinal motion; and being willing to participate in a genetic study of AS. Patients with a history of inflammatory bowel disease or psoriasis were not excluded. A total of 302 men and 100 women with AS met these inclusion criteria and were studied.

Clinical features

All participants completed extensive questionnaires about their medical and personal histories, and at each site one of the study rheumatologists performed a clinical evaluation on each participant. Clinical data included age, sex, ethnicity (white vs other), educational level, marital status, smoking status (current, former or non-smoker), pack years of smoking and comorbid medical conditions. Participants also reported their level of recreational physical activity in their teens and twenties, relative to their same-sex peers. An occupational physical activity score for each patient was computed, based on the level of physical activity (little, moderate, much) in each job they had worked at and the number of years spent in each job.¹¹ Additional data included duration of AS, age at onset of AS symptoms, family history of AS in a first-degree relative, history of total hip arthroplasty, history of iritis and human leucocyte antigen (HLA)-B27 status. Past and current medication history

Abbreviations: AS, ankylosing spondylitis; BASFI, Bath Ankylosing Spondylitis Functional Index; BASRI, Bath Ankylosing Spondylitis Radiographic Index; BASRI-spine, Bath Ankylosing Spondylitis Radiographic Index Spine; HAQ-S, Health Assessment Questionnaire for the Spondyloarthropathies; HLA, human leucocyte antigen; PSOAS, Prospective Study of Outcomes in Ankylosing Spondylitis

Table 1 Clinical features are compared between men and women with ankylosing spondylitis from the Prospective Study of Outcomes in Ankylosing Spondylitis cohort

	Men (n=302)	Women (n=100)	p Value
Age, years	55.5 (10.6)	53.0 (11)	0.04
Mean (SD) age at onset, years	23.6 (7.9)	21.5 (7.3)	0.03
Mean (SD) duration of AS, years	32.0 (9.9)	31.5 (10.1)	0.67
Family history	24.6%	41.0%	0.002
Smoking status			
Current	11.6%	8%	0.003
Former	49.0%	33.0%	
Never	39.4%	59.0%	
Mean (SD) education level, years	16.0 (3.1)	15.9 (2.7)	0.70
Weighted occupational physical activity*	1.8 (0.7)	1.9 (0.7)	0.61
Married	65.6%	65.0%	0.92
Ethnicity			
White	88.1%	87.0%	0.79
Black	3.6%	5.0%	
Asian/Pacific Islander	1.7%	3.0%	
Native American	1.3%	0%	
Hispanic	4.9%	4.0%	
Other	0.3%	1.0%	
HLA-B27-positive	88.7%	84.0%	0.22

*1–3 light to heavy.

AS, ankylosing spondylitis; HLA, human leucocyte antigen.

included the use of methotrexate, sulphasalazine, intra-articular steroids, prednisone, infliximab and etanercept. A history of peripheral arthritis was not collected because such information would not be verifiable or valid.

Functional status

To measure functional disability, participants were asked to complete both the Bath Ankylosing Spondylitis Functional Index (BASFI)¹² and the Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S).¹³ Both the BASFI and the HAQ-S have been demonstrated to have good reliability and construct validity.^{12–17} The BASFI is a 10-item scale on which respondents rate the degree of difficulty they have in performing certain tasks, using visual analogue scales from 0 (easy) to 100 (impossible). The mean of the 10 responses is the BASFI

Table 2 Comparison of drug usage between men and women with ankylosing spondylitis from the Prospective Study of Outcomes in Ankylosing Spondylitis cohort

	Men (n=302) (%)	Women (n=100) (%)	p Value
Past intra-articular steroid use	31.8	49	0.002
Sulphasalazine use			
Past	32.1	47	0.008
Current	6.6	11	0.16
Methotrexate use			
Past	17.2	25	0.09
Current	5.6	8	0.40
Prednisone use			
Past	28.5	48	0.003
Current	3.6	10	0.02
Infliximab use			
Past	7	14	0.04
Current	5	10	0.08
Etanercept use			
Past	16.2	12	0.31
Current	11.9	8	0.28

score. The HAQ-S is a 25-item scale on which respondents rate the degree of difficulty they have performing tasks in 10 functional areas, with responses ranging from 0 (no difficulty) to 3 (unable to do). The average of the highest score in each of the 10 function categories is the HAQ-S score.

Radiographs

Radiographs of the pelvis (anterior–posterior), lumbar spine (anterior–posterior and lateral) and cervical spine (lateral) were obtained from each participant and were scored using the Bath Ankylosing Spondylitis Radiographic Index Spine (BASRI-spine) score¹⁸ by a single musculoskeletal radiologist (TJL). The range of scores for the BASRI-spine is 2–12. Inter-reader and intra-reader reliability testing for BASRI scoring was performed on a subset of radiographs, with adjudication between all investigators for inclusion and exclusion of subjects. The BASRI was the best characterised and most standardised instrument available at the time this study started; the statistical adjustments below were made for its limitations.

Statistical analysis

The unadjusted male–female comparisons were done using *t* tests for continuous measures that were normally distributed Wilcoxon's rank sum tests for continuous measures that were not normally distributed, and χ^2 tests for categorical measures. For the analysis of radiographic data, the BASRI-spine score was considered an ordered categorical variable. As some scores had few patients and the BASRI-spine scores are known to be subject to a ceiling effect,¹⁹ the BASRI-spine scores were grouped into six ordered categories: 2–4, 4.5–6.5, 7–8.5, 9–10, 11–11.5 and 12. Odds ratios (ORs) for association of gender with the BASRI-spine category were calculated by ordinal logistic regression. These ORs represent the likelihood that men were more likely than women to be in a higher BASRI-spine category (1–6) than in the same or in a lower category. Multivariate modelling of the association of gender with BASRI-spine category included either age or duration of AS in separate models, because age and duration were strongly correlated in this cohort. Additional variables in the age-adjusted models were weighted occupational physical activity score, family history and pack years of smoking, while additional variables in the duration-adjusted models were age of onset, weighted occupational physical activity score, family history and pack years of smoking. The associations of BASRI-spine scores with functional measures were performed using Spearman's correlation coefficients.

Literature review

For the literature review, a MEDLINE search from 1966 to 2005 was performed, including the terms "ankylosing spondylitis", "men", "women" and "gender". The studies published before 1966 that are included in the review were identified in the bibliographies of the selected articles. To be included, the study had to report results comparing clinical and/or radiographic features between men and women. Comparisons of specific clinical and radiographic features were examined separately, and the results were summarised.

RESULTS

Clinical features and outcomes

In total, 302 men and 100 women with AS were studied in this cohort. Women had a significantly earlier age at disease onset, but the disease duration at the time of study entry was nearly equal between the genders (table 1). Women more frequently reported family histories of AS in first-degree relatives than men. Men were more likely to be current or former smokers.

Table 3 Associations of male gender with Bath Ankylosing Spondylitis Radiographic Index Spine score category from the Prospective Study of Outcomes in Ankylosing Spondylitis cohort, with adjustments for age or duration of ankylosing spondylitis and multivariate modelling*

Independent variable	Age-adjusted OR (95% CI)	p Value	Duration adjusted OR (95% CI)	p Value
Male	3.86 (2.53 to 5.90)	<0.001	4.10 (2.69 to 6.26)	<0.001
Multivariate analysis				
Male	3.81 (2.45 to 5.93)	<0.001	3.83 (2.46 to 5.96)	<0.001

*These ORs represent the likelihood that men were more likely than women to be in a higher BASRI-spine category than in the same or in a lower category.

There were no statistically significant differences in educational level, weighted occupational physical activity, marriage status, ethnicities or HLA-B27 positivity (table 1). The frequency of total hip arthroplasty between the two groups was not statistically different (9.6% of men vs 13% of women, $p = 0.34$). The frequency of iritis was not statistically different (42% of men vs 44% of women, $p = 0.74$). In terms of drug usage, women were significantly more likely to have been treated with intra-articular steroids, sulphasalazine in the past, prednisone in the past and currently, and infliximab in the past. More women had current or past use of methotrexate, but the values did not reach statistical significance (table 2).

Radiographic results

Radiographic severity was worse among men. The unadjusted median BASRI-spine score for men was 10 vs 6.5 for women ($p < 0.001$ by Wilcoxon’s rank sum test.) Adjusting for age, men were significantly more likely than women to be in a higher BASRI-spine category than in the same or a lower category, with an OR of 3.86 (95% CI 2.53 to 5.90, $p < 0.001$). After adjusting for duration of disease instead of age, the OR was still significantly high at 4.10 (95% CI 2.69 to 6.26, $p < 0.001$). In multivariate adjusted analyses, men were still more likely to be in a higher BASRI-spine category than women, with an OR of 3.81 (95% CI 2.45 to 5.93, $p < 0.001$) after adjusting for age and with an OR of 3.83 (95% CI 2.46 to 5.96, $p < 0.001$) after adjusting for duration of disease (table 3).

Functional outcomes

Functional limitations as measured by the BASFI were not statistically different between men and women in unadjusted analysis (table 4). Results comparing HAQ-S scores were comparable and also not statistically different (data not shown). Using analyses adjusted for age, duration of AS or the above multivariate model, the results were still not statistically different for both the BASFI and HAQ-S scores (data not shown). However, including the BASRI-spine scores in the multivariate model revealed that women had statistically significant worse functional scores as measured by both BASFI (table 4) and HAQ-S (data not shown), thus indicating that, at

the same level of radiographic damage, women had worse functional scores. The results of an additional analysis, which was performed to evaluate the associations of BASRI-spine scores with functional measures in men and women, using Spearman’s correlation coefficients, revealed that radiographic damage has a similar correlation with functional impairment in men and women (table 5). Thus, although radiographic damage correlates with functional impairment in men and women, women report more functional limitations at the same level of radiographic damage.

Literature search results

In all, 14 studies comparing clinical features and 13 studies comparing radiographic features of men and women with AS were identified.^{1 2 14 18 20–32}

Clinically, the most consistent trends that emerged were that women had more neck and peripheral joint pain (table 6). Several studies examined root joints (hips and shoulders) separately, whereas others considered them all together. The remarks on overall course tended to describe women as having either the same or milder course, although these conclusions were not based on objective measurements.

In terms of radiographic differences (table 7), the features that stood out from the literature review are that women tend to have less thoracic and lumbar spinal radiographic severity, and in the more recent studies, lower BASRI scores. The studies that looked specifically at findings on cervical spine and peripheral joints (including hip and shoulder), however, did not report evidence of women having more radiographic damage in these areas. Thus, the literature review data of clinical differences indicating increased pain in the cervical spine and peripheral joints did not necessarily correlate with radiographic changes.

The studies done before 1976 used no criteria for patient inclusion,^{20–23} and of the remaining studies, only the study by Kidd *et al*³⁰ used the modified New York criteria. Furthermore, the earlier of these studies did not use statistical methods to quantify their observations, and their conclusions were only qualitative.^{20–24} In later studies, statistical comparisons were

Table 4 Comparison of functional outcomes between men and women with ankylosing spondylitis from the Prospective Study of Outcomes in Ankylosing Spondylitis cohort

	Men (n = 302)	Women (n = 100)	p Value
Mean BASFI score, unadjusted	40.6	41.7	0.73
BASFI score, adjusted mean (SEM) (using age, multivariate model and BASRI-spine score)	43.3 (2.1)	49.0 (2.9)	0.05

BASFI, Bath Ankylosing Spondylitis Functional Index; BASRI-spine, Bath Ankylosing Spondylitis Radiographic Index Spine score.

Table 5 Correlation between Bath Ankylosing Spondylitis Radiographic Index Spine scores and Bath Ankylosing Spondylitis Functional Index scores in men and women (Spearman’s correlation coefficients)

	BASFI	p Value
BASRI-spine, all patients	0.32	<0.001
BASRI-spine, men	0.35	<0.001
BASRI-spine, women	0.32	0.002

BASFI, Bath Ankylosing Spondylitis Functional Index; BASRI-spine, Bath Ankylosing Spondylitis Radiographic Index Spine score.

Table 6 Clinical comparisons of women with men from prior ankylosing spondylitis studies in the literature*

	Age of onset	Iritis	Cervical spine pain	Thoracic and lumbar spine pain	Hip/shoulder pain	Peripheral joint pain	Overall course	Number of men	Number of women
Gran <i>et al</i> , 1985 ⁵	Same	Same	Less	Same		Same	Same	82	44
Will <i>et al</i> , 1990 ²	Older	Same			More	More		1202	498
Tyson <i>et al</i> , 1953 ²⁰			More		Same	Same	Same		60
Hart <i>et al</i> , 1959 ²¹	Same						Milder		30
McBryde <i>et al</i> , 1973 ²²	Older								13
Levitin <i>et al</i> , 1975 ²³				Less		More	Same		9
Resnick <i>et al</i> , 1976 ²⁴	Older		More	Less		More	Milder	80	18
Spencer <i>et al</i> , 1979 ²⁵							Same	164	36
Braunstein <i>et al</i> , 1982 ²⁶	Same		Less	Less		More	Milder	31	32
Marks <i>et al</i> , 1983 ²⁷	Same	More	More		More	More		25	25
Maldonado-Cocco <i>et al</i> , 1985 ²⁹		Less	More					34	18
Kidd <i>et al</i> , 1988 ³⁰	Same	Same	Same	Same	Less	Same		70	35
Jimenez-Balderas <i>et al</i> , 1993 ³¹	Same	Same		Same	Same	Same	Same	41	41
Eustace <i>et al</i> , 1993 ³²						More		64	19

*The results are given for women compared with men. See the text for further detailed descriptions of the studies.

made, but multivariate adjustments were not in use until the late 1980s.^{2 14 18 30-32} Frequently, the studied cohorts had wide ranges of disease durations and age ranges among the patients. Finally, most of these studies were carried out using retrospective chart review, except for two case-control studies^{29 30} and one questionnaire study.²

DISCUSSION

The focus of this study on patients with longstanding disease gives an advantage in terms of reducing the confounding influence of large differences in AS duration, by examining patients at a time when the course of their AS had largely been established. However, a limitation is that the results are conditional on the fact that these are all patients with

longstanding AS, and their results may not necessarily be generalisable to patients with early AS. In addition, this cohort is a convenience sample and is not community-based, and thus may not represent the entire AS community.

The review of earlier studies showed that women had more peripheral arthritis and fewer spinal radiographic changes. However, a number of problems with methodological issues limits the conclusions that can be drawn from those studies. In our study, we found differences in usage of intra-articular steroids, sulphasalazine and prednisone, which could suggest more peripheral arthritis in women with AS. Alternatively, these women with AS may have presented with peripheral arthritis and been considered to have a primary peripheral arthritis before AS was apparent or diagnosed. Our finding that

Table 7 Radiographic comparisons of women with men from prior ankylosing spondylitis studies in the literature*

	Cervical spine	Thoracic and lumbar spine	Peripheral joints	Hip/shoulder	BASRI	Number of men	Number of women
Will <i>et al</i> , 1990 ²	Same	Less		Same		1202	498
Calin <i>et al</i> , 1999 ¹⁸	Less	Less		Same	Less	354	72
Doran <i>et al</i> , 2003 ¹⁴					Less	254	57
Tyson <i>et al</i> , 1953 ²⁰							60
Hart <i>et al</i> , 1959 ²¹	Same	Less					30
Levitin <i>et al</i> , 1975 ²³		Less					9
Resnick <i>et al</i> , 1976 ²⁴	More	Less	Same			80	18
Spencer <i>et al</i> , 1979 ²⁵		Less	More			164	36
Braunstein <i>et al</i> , 1982 ²⁶	Less	Less	Same	Same		31	32
Gran <i>et al</i> , 1984 ²⁸		Less				82	50
Kidd <i>et al</i> , 1988 ³⁰		Less				70	35
Jimenez-Balderas <i>et al</i> , 1993 ³¹		Less				41	41
Eustace <i>et al</i> , 1993 ³²	Same	Same				64	19

*The results are given in terms of the involvement of the listed area in women as compared with men. See the text for further detailed descriptions of the studies.

more women with AS had positive family histories of AS could suggest that the diagnosis of AS may be made more often in women when suspicion for AS is heightened.

Although our study confirms the earlier finding that men have more radiographic damage than women, it also allows us to be more nuanced than the earlier studies in that our data show that women have more functional limitations for a given level of radiographic damage. There seemed to be an apparent contradiction in that although the radiographic outcome was significantly different between men and women, the functional outcomes were the same. However, an analysis of the associations of BASRI-spine scores with functional measures in men and women showed that radiographic damage has a similar correlation with functional impairment in both men and women. Additional analyses of associations of men and women with functional measures after adjusting for BASRI-spine scores showed that, for a given degree of radiographic damage, women reported more functional limitations.

Gran *et al.*'s study¹ showed that there were no differences between men and women with AS in terms of spinal mobility.¹ Another study of patients with AS found that the changes in spinal mobility do not explain the observed differences in function.³³ In addition, the relationship between the accumulation of spinal radiographic damage and corresponding function in AS remains unknown. Even among the studies in rheumatoid arthritis that have examined this issue more extensively, the nature of the connection between radiographic damage and functional loss is controversial and may differ over the time course of the disease.^{34–36} This discrepancy between radiographic damage and reporting of function may be a result of women having more peripheral arthritis. For example, patients with lower extremity (ie, knee) problems would be more likely to have lower function scores.³⁷

The underlying pathogenesis of the differences between men and women with AS is unknown. The prevalence of HLA B27 among women with AS is equivalent to that in men,³ and no linkage of the X chromosome with susceptibility to AS was found.^{38–39} However, a direct genetic difference in the ankylosis homologue (ANKH) gene between men and women with AS has been recently described by Tsui *et al.*⁴⁰ Further genetic studies may reveal more genes that are involved in the prevalence and severity of AS.

In conclusion, there are differences in the expression of AS between the genders. We observed that, among patients with longstanding AS, there are treatment differences between the genders that suggest that women may have more peripheral arthritis. Men have significantly more severe radiographic changes in spite of similar disease duration. We found that, at any given level of radiographic damage, women report worse functional outcomes. All of these findings suggest that the phenotype of AS differs between the genders, and this may influence the manner and timing of the diagnosis of AS as well as the choice and timing for initiation of treatment.

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