The Interrelationship Between Sex, Susceptibility Factors, and Outcome in Ankylosing Spondylitis and Its Associated Disorders Including Inflammatory Bowel Disease, Psoriasis, and Iritis

SINEAD BROPHY, GORDON TAYLOR, DAVID BLAKE, and ANDREI CALIN

ABSTRACT. ***Objective.*** To examine the evidence that families, where the mother has disease, carry more heritable factors and investigate the effect of maternal/paternal inheritance on phenotypic expression of disease in terms of (a) severity and outcome and (b) additional co-disorders. The children of women with ankylosing spondylitis (AS) develop the disease more often than the children of men. This suggests that either women with disease carry more susceptibility factors than men or that the uterine environment/breast feeding may play a role in AS.

Methods. The number of second degree relatives (i.e., grandparent, aunt/uncle) was calculated for those index patients with a mother with disease as opposed to a father. Outcome measures were compared and prevalence of secondary disorders (i.e., psoriasis, iritis, inflammatory bowel disease) was examined in patients with an AS mother as opposed to an AS father.

Results. The affected offspring of maternal cases had more second degree relatives with disease [20% vs 9%, respectively, p = 0.012, odds ratio (OR): 2.3, 95% confidence interval (CI): 1.2, 4.5] than did children of affected men. The affected children of a mother with AS were comparable in terms of disease activity, function, and radiology to children of a father with disease. Inflammatory bowel disease was more prevalent among children of AS mothers than AS fathers (15% vs 5%, respectively, p = 0.009, OR: 2.9, 95% CI: 1.3, 6.3). Psoriasis was less prevalent among sons of AS mothers than among sons of AS fathers (9% vs 22%, respectively, p = 0.03, OR: 0.4, 95% CI: 0.2, 0.9).

Conclusion. The inherited susceptibility load is strongly linked to the sex of the parent with AS. Women with disease carry higher heritability (which is associated with inflammatory bowel disease) than do men. There is a male sex impact on susceptibility to psoriasis (when AS is present). However, there is no evidence that the susceptibility load has an effect on outcome or severity of disease (as measured by disease activity, function, and radiology), or that outcome is influenced by transmission of maternal as opposed to paternal factors. (J Rheumatol 2003;30:2054–8)

Key Indexing Terms:
SPONDYLITIS OUTCOME MATERNAL TRANSMISSION
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Ankylosing spondylitis (AS) is a polygenic disease[1]. The link between susceptibility to spondyloarthropathy and the gene HLA-B27 has been recognized for 25 years[2]. Approximately 10% of random HLA-B27 positive subjects develop AS[3,4]. However, this risk is significantly greater among the B27 positive family members of affected patients[4]. Yet the HLA genes can only explain one-third of the genetic influence seen in AS[5]: many other genes found in different areas of the genome are also involved[6-8].

It is known that there are differences in the way men and women are affected by AS. A greater number of men develop the disease (2.5:1, males:females) and they also develop more severe spinal disease[9]. Women have increased levels of disease activity (pain, fatigue, discomfort)[10] and the children of female patients are affected by the disease more frequently than those of male patients[11,12]. Furthermore, the offspring of women who developed AS at a young age are more likely to develop the disease than those whose mothers developed disease later in life[11]. One explanation for this is a genetic load effect. In general, women are less likely than men to develop AS. Thus, it remains possible that women with AS have to have a higher

From the Epidemiology Department, Royal National Hospital for Rheumatic Disease, Upper Borough Walls, Bath, UK.

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S. Brophy, PhD, Research Officer; G. Taylor, PhD, Biostatistician; D. Blake, FRCP, Professor of Bone and Joint Medicine; A. Calin, MD, FRCP, Consultant Rheumatologist.

Address reprint requests to Dr. A. Calin, Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath BA1 1RL, UK. E-mail: andrei.calin@virgin.net

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genetic load in order to develop disease. This higher genetic load (i.e., susceptibility genes) is passed on to the children, causing them to develop AS. Alternatively, factors such as the uterine environment and breast feeding may impact on susceptibility to disease.

Our study is based on the hypothesis that women require a higher susceptibility gene load in order to develop AS: the son of an AS father may inherit enough genes to predispose a man to the disease, but any daughter of that AS father with disease may not inherit enough susceptibility factors and therefore will not develop AS. Any female who does develop disease must, by definition, carry enough susceptibility factors to show clinical symptoms of disease. This would suggest that although mothers carry more susceptibility genes, the daughter of a man with disease may be comparable to the daughter of a woman with disease, in terms of genetic susceptibility load. Therefore, the effect of susceptibility genes on severity can only be seen by examining the sons of AS mothers (who have a greater susceptibility load) compared to sons of AS fathers (who have a lower susceptibility load).

We examined (1) evidence that families where the mother has disease carry more heritable factors than families where the father has AS and (2) the effects of maternal versus paternal inheritance on disease severity (as measured by disease activity, function, radiology, and prevalence of secondary disorders, i.e., iritis, bowel disease, and psoriasis).

MATERIALS AND METHODS

The Bath AS Database consists of 5507 (M:F, 2.5:1) patients. All are outpatients at the Royal National Hospital for Rheumatic Diseases (RNHRD) or are members of the National Ankylosing Spondylitis Society (NASS). Patients referred to the RNHRD had their diagnoses confirmed according to the New York Criteria. The NASS members are those who have received a diagnosis of AS from a specialist rheumatologist as a result of a pelvic radiograph. To validate the diagnosis in those patients recruited through NASS, 240 patients were randomly selected and a confirmation of diagnosis was sought from the general practitioner and confirmed in 229 cases (95.4%) (i.e. AS with radiological evidence of sacroiliitis). To validate the diagnosis of secondary disease, we contacted the general practitioners of 120 patients with psoriasis-AS and 139 patients with inflammatory bowel disease-AS (IBD-AS). Of these, 77 (64%) and 112 (81%), respectively, replied confirming the diagnosis of psoriasis and IBD in 65 (84%) and 108 (96%) of cases, respectively. All patients with a family history of AS were then selected and a confirmation of the diagnosis was sought for each. Only those patients with a confirmed diagnosis were selected for the study.

Susceptibility. The number of affected second generation relatives (reported by patient) of AS children with an AS affected mother was calculated and compared to number of affected relatives for children with an AS affected father (one randomly selected AS child was used per family). This analysis should highlight whether AS mothers inherit more genetic factors relating to susceptibility to AS. Women are more likely to have first degree relatives with AS (i.e., children and siblings)[11], but it is not clear if there is a greater rate of a previous family history of disease among women.

Severity. The outcome measures for children of an AS mother were compared to those of an AS father (one member per family was selected, affected siblings were removed). Measures used were disease activity (Bath Ankylosing Spondylitis Disease Activity Index calculated on a 0-10 scale[13]), function (Bath Ankylosing Spondylitis Functional Index calculated on a 0-10 scale[14]) and radiology (Bath Ankylosing Spondylitis Radiology Index calculated on a 2-16 scale[15]).

Sons of AS mothers were compared to sons of AS fathers for prevalence of secondary disease (iritis, psoriasis, IBD). This analysis was repeated for daughters of AS mothers compared to those of AS fathers.

Statistical methods. SPSS version 10 was used for all analysis. Data were tested for normality and t tests were used to compare number of women with a previous family history compared to men and to compare severity of disease among the children of men and women with disease. The chi-square test was used to examine the prevalence of secondary disease among offspring of AS men and women. Odds ratios (OR) are presented for 95% confidence intervals (CI).

RESULTS

There were 328 children of AS parents with a confirmed diagnosis of AS. Of these the B27 status was available on 44 (43/44 were positive) and sacroiliac joint radiographs were requested and scored on 90 randomly selected subjects, all of whom were found to have evidence of sacroiliitis of grade 2 or more.

Susceptibility. There were 203 patients with an AS father and 125 patients with an AS mother. The offspring of women with disease had more previous generation AS relatives (grandparents, uncle/aunt) than the offspring of men with disease ($p = 0.012$, OR: 2.3, 95% CI: 1.2, 4.5) (Figure 1). These cohorts were comparable for disease duration and age. In addition, if a daughter of an AS father was affected, there was also a greater chance that there was a previous generation family history than if the son was affected (i.e., 13% of daughters compared to 7% of sons).

There were 25 patients (20%) with an AS mother and 19 patients (9%) with an AS father who had a previous family history. For children of AS fathers, 10/76 (13%) of daughters and 9/125 (7%) of sons had additional relatives. For children of AS mothers, among daughters there were 13/57 (22%) who had other AS relatives compared to 12/68 (18%) of sons (Figure 1).

Severity. The children of a mother with AS were comparable in terms of disease activity, function, and radiology to those of a father with disease (Table 1).

Daughters of AS mothers and fathers had worse disease activity and function than sons of AS mothers and fathers (i.e., gender of the patient and not gender of the parent influenced outcome) (Table 2). For example the disease activity for a daughter of a man with AS was 53% worse than that for a son of a man with AS. The disease activity for the daughter of a woman with AS was 23% worse than the son of a woman with AS.

The prevalence of iritis is comparable between children of female AS patients compared to male patients (33%-39%). However, IBD is more prevalent among children of AS mothers (19/123, 15%) than among AS fathers (10/196, 5%, $p = 0.009$, OR: 2.9, 95% CI: 1.3, 6.3). Conversely, psoriasis is less prevalent among sons of AS mothers than

Table 1. Impact of sex on inheritance of disease expression.

AS Female	With AS Mother	With AS Father	t test
n	57	76	
Disease duration (SD)	15.9 (± 11.5)	16.2 (± 9.1)	0.3 [–3.0–3.8]ns
Age (SD)	38.6 (± 11.3)	37.2 (± 10.8)	1.4 [–2.7–4.9]ns
Disease activity, BASDAI (SD)	4.3 (± 2.9)	4.9 (± 2.3)	0.7 [–0.2–1.6]ns
Function, BASFI (SD)	3.7 (± 3.2)	3.8 (± 3.4)	0.2 [–0.9–1.4]ns
AS Male	With AS Mother	With AS Father	
n	68	127	
Disease duration (SD)	18.8 (± 11.3)	15.9 (± 9.9)	2.9 [–0.2–6.0]ns
Age (SD)	40.5 (± 12.7)	38.1 (± 11.0)	2.5 [–0.9–6.0]ns
Disease activity, BASDAI (SD)	3.5 (± 2.7)	3.2 (± 3.3)	0.3 [–0.7–1.2]ns
Function, BASFI (SD)	3.0 (± 3.4)	2.8 (± 2.6)	0.2 [–0.6–1.1]ns
Patient	With AS Mother	With AS Father	
n	22	39	
Disease duration (SD)	15 (± 10.1)	17 (± 10.8)	
Age (SD)	37 (± 12.4)	41 (± 11.3)	
BASRI (SD)	5.8 (± 4.7)	6.2 (± 3.3)	0.4 [–1.6–2.6]ns

BASDAI: Bath AS Disease Activity Index; BASFI: Bath AS Functional Index; BASRI: Bath AS Radiology Index.

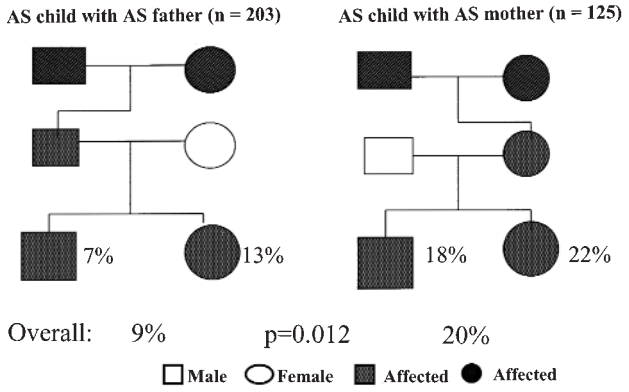

Figure 1. Percentage of index children (mother/father with disease) with a second degree relative with AS. AS affected children of AS mothers are more likely to have secondary degree relatives (i.e., 20% to 9%) than children of AS fathers. Therefore, AS affected women carry more susceptibility genes than AS affected men. Similarly, when daughters of AS men are affected there is more likely to be a second degree family history than when sons are affected. Shaded symbols indicate affected subjects.

among sons of AS fathers (p = 0.03, OR: 0.4, 95% CI: 0.2, 0.9) (Table 3).

Of the 29 children with IBD the records of the parents were available in 14 (48%) cases. Only 1 of the 14 (7%) affected parents of IBD-AS children also suffered from IBD. Of the 38 children with psoriasis and an AS father the records of the parent were available in 19 (50%) cases. There were 6/19 (32%) cases of psoriasis among the AS affected fathers.

DISCUSSION

Our study examines (1) whether the increased inheritance of AS among the children of affected mothers could be due to environmental factors (e.g., uterine environment or breast feeding) or whether there is evidence for a higher susceptibility gene load within these families and (2) the effect of maternal transmission of disease compared to paternal transmission.

Families where the mother and child have disease appear to carry more heritable factors predisposing the family to disease than father-child families. Approximately 20% of patients with an AS mother compared to 10% of children of AS fathers, had second generation relatives with disease.

Table 2. Disease severity of children of parents with AS.

Mother	Daughter, mean (SD)	Son, mean (SD)	Difference (confidence intervals)
Disease activity, BASDAI	4.3 (2.9)	3.5 (2.7)	0.8 (0.2–1.6)
Function, BASFI	3.7 (3.2)	3.0 (3.0)	0.7 (–0.2–1.8)
Father			
Disease activity, BASDAI	4.9 (2.3)	3.2 (3.3)	1.7 (0.6–1.8)
Function, BASFI	3.8 (2.7)	2.8 (2.6)	1.0 (0.3–1.8)

BASDAI: Bath AS Disease Activity Index; BASFI: Bath AS Functional Index.

In terms of disease activity, function, and radiology, there is no difference between disease transmitted from the maternal side compared to that from the paternal side. The level of susceptibility should be comparable between daughters of mothers with AS and fathers with AS. However, sons of AS fathers should carry fewer susceptibility genes than sons of AS mothers. The finding that AS sons inheriting disease from the maternal side do not differ from sons inheriting disease from the paternal side might suggest that susceptibility effects (predisposition to disease) do not impact on the outcome or severity of disease. That susceptibility factors are not associated with altered severity may be supported by findings that in the transgenic ank/ank mouse, the susceptibility gene HLA-B27 plays no part in the phenotypic expression of ankylosis[16]. Among patients, HLA-B27 is associated with younger age at onset but not with severity measures as determined by clinical and radiological variables[17].

Women with AS report more disease activity and poorer function than AS men. However, a mother with AS did not transmit to her son worse disease activity/function and fathers with AS did have AS daughters with improved disease activity/function. Thus, the disease activity and function reflects the gender of the patient and not of the parent with AS.

IBD is more likely to be inherited by the children if the mother had AS. However, only 7% of the traced mothers of patients with AS-IBD had concomitant bowel disease. Psoriasis was inherited more by sons of AS fathers than by those of AS mothers. Among patients with psoriasis, it has been shown that paternal transmission of psoriasis is higher than maternal transmission[18,19]. In this case, 32% of the fathers also had psoriasis. The sex ratio in uncomplicated psoriasis and uncomplicated IBD is virtually one to one[20]. More women with AS have bowel disease than expected and more men with AS have psoriasis. Among this sample of patients women do not appear to be protected from psoriasis (as 15% to 17% have the disease). However, male offspring of male AS patients appear most at risk, perhaps because the father may be more likely to have psoriasis. Offspring of women with AS develop more IBD even when the mothers do not seem to have the condition. Iritis is inherited equally from mother and father, perhaps because it is strongly linked to the HLA-B27 gene that most patients with AS carry.

For women to develop AS, some of the susceptibility genes they need may overlap with those for IBD. These genes are passed on to the children so women appear to carry more of these occult or expressed bowel disease genes.

The number of susceptibility genes inherited by the children are very strongly linked to the gender of the parent. Women carry a higher susceptibility load and this load contains factors associated with IBD. There is a male gender effect on susceptibility to psoriasis when AS is present. However, there is no evidence that susceptibility load has an

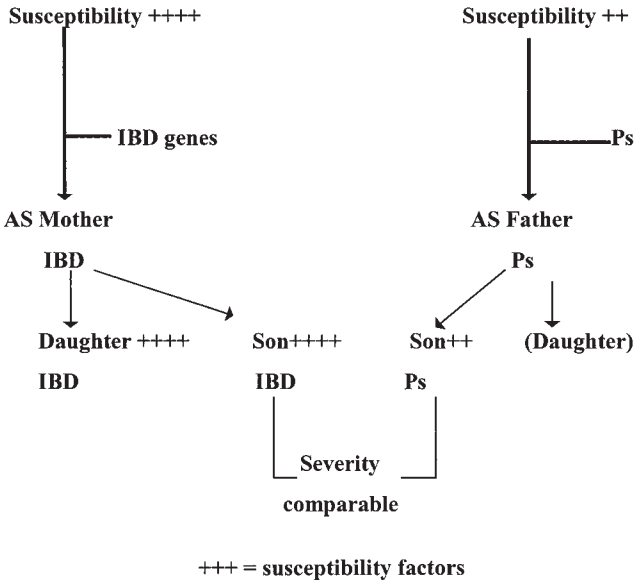

Figure 2. AS women carry more susceptibility genes but their children do not have more severe disease than AS men. Therefore, susceptibility factors have no bearing on severity or outcome of AS.

Table 3. Daughters and sons of AS affected mothers or AS affected fathers compared for prevalence of secondary disease (iritis, psoriasis, and inflammatory bowel disease).

AS Female	With AS Mother	With AS Father	Odds Ratio
n	57	76	
Disease duration (SD)	15.9 (± 11.5)	16.2 (± 9.1)	
Age (SD)	38.6 (± 11.3)	37.2 (± 10.8)	
Iritis (n)	33% (19)	39% (30)	0.8 [0.4–1.6]
Psoriasis (n)	15% (9)	17% (13)	0.8 [0.3–2.1]
Inflammatory bowel disease (n)	18% (10)	6% (4)	3.7 [1.1–12.6] p = 0.03
AS Male	**With AS Mother**	**With AS Father**	**Odds Ratio**
n	68	127	
Disease duration (SD)	18.8 (± 11.3)	15.9 (± 9.9)	
Age (SD)	40.5 (± 12.7)	38.1 (± 11)	
Iritis (n)	36% (24)	34% (43)	1.1 [0.6–2.1]
Psoriasis (n)	9% (6)	22% (28)	0.4 [0.2–0.9] p = 0.03
Inflammatory bowel disease (n)	13% (9)	5% (6)	2.9 [1.0–8.7] p = 0.05

effect on outcome and severity of disease (as measured by disease activity, function, and radiology), or that outcome is influenced if the transmission is maternal as opposed to paternal (Figure 2).

Our results show that families where the mother has AS contain more heritable factors than families with an AS father. In addition, disease transmitted from the maternal side does not differ from disease transmitted from the paternal side in male patients in terms of severity. In terms of susceptibility, however, disease among female patients may differ, as there are fewer susceptibility genes from the paternal side and daughters are less likely to develop the condition. Offspring of women with AS develop more IBD and sons of men with AS develop more psoriasis, indicating that there is a gender effect on inheritance of secondary conditions associated with AS.

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