Concordance of Disease Severity Among Family Members with Ankylosing Spondylitis?

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ABSTRACT. ***Objective.*** The heritability of disease activity and function in ankylosing spondylitis (AS) have been estimated at 0.51 and 0.63 (i.e., 51% and 63%), respectively. We examined the concordance of disease severity among family members in terms of disease activity, function, radiological change, prevalence of iritis, and juvenile onset.

Methods. Disease activity and functional impairment due to AS were studied using the Bath AS Disease Activity Index (BASDAI) and Functional Index (BASFI) self-administered questionnaires; radiographic involvement was measured using the Bath AS Radiology Index (BASRI) scale. Familial correlation of BASDAI and BASFI was assessed in 406 families with 2 or more cases, using the program PAP. Parent–child and sibling–sibling concordance for iritis and juvenile AS were also studied in these families. Heritability of radiological disease severity based on the BASRI was assessed in 29 families containing 60 affected individuals using the program SOLAR.

Results. Correlations between parent–child pairs for disease activity and function were 0.07 for both. Correlations between sibling pairs for disease activity and function were 0.27 and 0.36, respectively. The children of AS parents with iritis were more likely to develop iritis [27/71 (38%)] than children of non-iritis AS parents [13/70 (19%)] ($p = 0.01$). Parents with JAS were more likely to have children with JAS [17/30 (57%) compared to non-JAS parents 34/111 (30%)] ($p = 0.002$). The heritability of radiological disease severity based on the BASRI was 0.62.

Conclusion. While correlation in severity between parent and child is poor, siblings do resemble each other in terms of severity, supporting the findings of segregation studies indicating significant genetic dominance in the heritable component of disease activity. Significant parent–child concordance for iritis and juvenile disease onset suggest that there are genetic risk factors for these traits independent of those determining the risk of AS itself. The finding of significant heritability of radiological change (BASRI) provides support using an objective measure for the observed heritability of the questionnaire-assessed disease severity scores, BASDAI and BASFI. (J Rheumatol 2004;31:1775–8)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS SEVERITY INHERITANCE

Ankylosing spondylitis (AS) is a common chronic inflammatory arthritis that typically develops in the late teens or early twenties. Susceptibility to disease is determined by genetic background and possibly exposure to an external trigger. It is characterized by enthesitis, changes to the sacroiliac joints of the pelvis and fusion of the vertebrae of the spine, and can affect the hips and peripheral joints (i.e., hands, feet, knees, shoulders)[1]. AS is associated with inflammation of the eye, skin and bowel, and in rare cases can affect the heart and lungs. The changes in the spine (i.e., back and neck), hip, and pelvis can be seen using radiographs and classified or scored using the Bath Ankylosing Spondylitis Radiology Index (BASRI)[2]. Previous work[3] with this scoring system has shown that severe radiological change is associated with male sex, disease duration, and the presence of iritis (inflammatory eye disease). The amount of change seen in the neck is more severe in cases with hip disease. However, these factors only account for 23% of the total variation seen in radiological change, and neither environmental nor clinical variables significantly influence BASRI[3]. Using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[4] and Functional Index (BASFI)[5], the heritabilities of disease activity and function in AS were

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estimated at 0.51 and 0.68, respectively[6]. These disease severity indices are assessed by self-administered questionnaire and are potentially subject to factors influencing questionnaire completion other than the disease status itself. In contrast, the heritability of disease severity assessed radiographically is more objective, but has not previously been studied. Heritability measures are difficult to translate into clinically relevant information about the likely severity of disease in affected relatives of index cases. Further, the familiality of iritis complicating AS, and juvenile onset of AS is unknown, although the age of disease onset is known to be heritable[7]. We examined the concordance of disease severity among family members in terms of disease activity, function, prevalence of iritis and juvenile onset, and assessed the heritability of radiographically assessed disease severity.

MATERIALS AND METHODS

The Bath Ankylosing Spondylitis Database includes data on 5507 AS cases (M:F 2.5:1). All subjects are outpatients of the Royal National Hospital for Rheumatic Diseases or are members of the National Ankylosing Spondylitis Society.

We studied all cases from the database reporting a family history of AS. In most cases the diagnosis was confirmed by both a qualified rheumatologist, as well as based on an interview by one of us, or by the individual's general practitioner. AS was defined according to the modified New York disease criteria[8], having both clinical and radiographic disease confirmation. Caring physicians were also asked to confirm if the patient had a diagnosis of iritis, psoriasis, or inflammatory bowel disease (IBD).

Individuals from 406 families including 325 affected sibling pairs, 213 affected parent–child pairs, and 51 other affected relative pairs were studied. Correlation of disease activity and function between parent–child and sibling–sibling pairs was assessed using the program PAP[9]. Covariates included sex and disease duration. Correlations between relative pairs were made by Fisher's z transformation.

The concordance rates for iritis and juvenile onset of AS (age of onset lower than 16 yrs) in children of affected and unaffected parents were assessed and compared using the chi-square statistic.

All subjects were compared for the effect on index case severity (in terms of disease activity and function) of: age of symptom onset, disease duration, delay in diagnosis, education, IBD, psoriasis, iritis, sex, and parental and sibling severity scores. Univariate analysis of variance was used to identify significant covariates of BASDAI and BASFI, which were then tested in a multivariate analysis to determine their independent contribution to disease severity.

The radiographs of 60 individuals from 29 families (4 parent–child pairs, 4 monozygotic twin pairs, 23 sibling pairs) were scored using the BASRI. New radiographs of the pelvis to include the hips and cervical and lumbar spine (both anterior-posterior and lateral views) were taken when there were no existing radiographs available. The majority of people consenting to the study did not have existing radiographs and this meant exposing them to radiation. We therefore stopped the study at 60 individuals as this number had the power to achieve statistical significance. Radiographs were scored by 2 trained independent readers (AM and SB) (kappa score for inter-observer variation: 0.74–0.76; intraobserver variation: 0.73–0.75). Discrepancies between scores were reviewed by a third trained reader (SH). The heritability of radiological disease severity based on the BASRI was evaluated using SOLAR[10], including sex and disease duration as covariates.

Our study was approved by the local ethics committee and all patients gave informed written consent prior to participation.

RESULTS

Disease severity and phenotype concordance. The correlations between parent and child for disease activity was 0.07 (i.e., almost no correlation). The correlation between sibling pairs for disease activity was 0.27 (i.e., 7% of the variance seen in one sibling is explained by shared factors with the other sibling). There was significantly more correlation between siblings than between parents and children ($p = 0.04$). The correlation between parent and child for function was 0.07 (almost none) and for siblings, 0.36 (13% of variance explained by shared factors). Again siblings showed significantly more correlation than parents and children ($p = 0.004$). In all cases the covariates included sex and disease duration.

The children of parents with iritis were more likely to develop iritis than children of parents with AS without this disorder (Table 1; 38% of children with an iritis parent had iritis compared to 19% of children with a non-iritis parent, $p = 0.01$).

The siblings of people with AS and iritis were more likely to have iritis than siblings of individuals with no iritis, although this trend failed to achieve statistical significance (Table 1; $p = 0.06$).

Parents with juvenile AS (JAS) were more likely to have children with juvenile onset (Table 2; 57% of AS-affected children of JAS parents had juvenile onset, compared with 30% of AS-affected children of parents with adult-onset AS, $p = 0.002$). However, there was no difference in the concordance rate in siblings (32% of JAS siblings had a sibling also with JAS compared to 27% of non-JAS siblings).

Determinants of disease severity in AS. Univariate analysis showed that determinants of disease activity included

Table 1. Comparison of family members with iritis. Results are expressed as proportions (%).

	Percentage with Iritis	
	AS Son	AS Daughter
Iritis mother	5/14 (36)*	6/15 (40)*
Non-iritis mother	2/13 (16)	5/15 (33)
Iritis father	11/28 (39)*	5/14 (36)*
Non-iritis father	3/22 (14)	3/20 (15)
	AS Brother	AS Sister
Iritis sister	7/14 (50)	7/10 (70)
Non-iritis sister	10/29 (34)	7/20 (35)
Iritis brother	19/43 (42)	8/13 (62)
Non-iritis brother	18/55 (32)	13/22 (59)

* Parents with iritis (average age 62.2 yrs) were more likely to have children with iritis [$p = 0.01$ 27/71 (38%) of parents with iritis had children with iritis compared to 13/70 (19%) of parents without iritis (average age 62.0 years)]. AS siblings of a person with AS-iritis are not significantly more likely to have iritis than siblings of a person without iritis [$p = 0.06$ 41/80 (51%) of siblings with a brother/sister with AS-iritis also had iritis compared to 39% of siblings with a brother/sister without iritis].

Table 2. Comparison of family members with juvenile age of symptom onset AS (JAS). Results are expressed proportions (%).

	Percentage with JAS	
	AS Son	AS Daughter
JAS mother	3/5 (60)*	4/7 (57)
Non-JAS mother	7/21 (33)	9/22 (40)
JAS father	5/10 (50)*	5/8 (63)*
Non-JAS father	9/40 (23)	9/28 (32)
	AS Brother	AS Sister
JAS sister	8/30 (27)	5/11 (45)
Non-JAS sister	14/63 (22)	10/26 (38)
JAS brother	6/15 (40)	1/7 (14)
Non-JAS brother	9/33 (27)	5/21 (24)

* JAS parents are more likely to have JAS children [p = 0.002, 17/30 (57%) JAS parents had JAS children compared to 34/111 (30%) of non-JAS parents who had JAS children].

education (p = 0.002), IBD (p = 0.01), and sibling disease activity (p = 0.008). Factors not related to disease activity were age of symptom onset (p = 0.5), disease duration (p = 0.2), delay in diagnosis (p = 0.7), parental disease activity (p = 0.9), iritis (p = 0.5), psoriasis (p = 0.6), and sex of the index case (p = 0.3). Multivariate analysis combining the significant factors into a model found education and IBD were no longer significant. Therefore, only sibling disease activity levels were found to be significant (p = 0.008), describing 10.5% of the variation in disease activity.

Univariate analysis showed that determinants of function were: education (p = 0.0001), disease activity (p = 0.001), disease duration (p = 0.003), and sibling functional level (p = 0.04). Factors not related to function were: age of symptom onset (p = 0.8), delay in diagnosis (p = 0.6), parental functional level (p = 0.3), IBD (p = 0.4), iritis (p = 0.9), psoriasis (p = 0.8), and sex of the index case (p = 0.4). Multivariate analysis combining the significant factors into a model found sibling functional level to be no longer significant. Therefore, education, disease activity, and disease duration were found to be significant ($p < 0.001$), contributing 50.7% of the variation in function. Disease activity accounted for 70% of the variation in BASFI explained by this model.

Heritability of radiological disease severity based on the BASRI. Heritability of radiological change was estimated at 0.62 (p = 0.04, standard error = 0.3). Sex and disease duration contributed significantly to the overall variance (p = 0.04 and $p < 0.001$ respectively) and were responsible for 36% of the overall variance.

DISCUSSION

Our study explores the concordance of family members for expression of severity in AS. Based on the self-administered questionnaire assessment of disease severity, little correlation was seen in parent–child pairs, but significant sibling–sibling similarity of disease severity was observed. The lack of similarity of parent–child pairs may reflect the difficulty of controlling for the large difference in disease duration across generations by comparison with sibling pairs, where the disease duration was much more similar. A potential genetic explanation would be the presence of a substantial genetic dominance determining the activity of AS. Dominance refers to effects due to interaction between alleles at a locus. As parent–child pairs only share one allele at any locus, they are not affected by genetic dominance. Sibling pairs, which may share 0, 1, or 2 parental alleles identical by descent, are affected by genetic dominance. Our own segregation study does suggest the presence of a major gene influencing disease severity, and that this gene has significant dominance[6]. Thus the segregation study findings predict that sibling correlation of disease severity would be greater than parent–child correlation, as we have observed in this study.

This study demonstrates significant familiality of iritis and juvenile onset of AS, over and above the susceptibility to AS. The relationship of iritis and AS is complex, as both conditions are associated with carriage of HLA-B27. The fact that each condition can occur in the absence of the other suggests differences in their risk factors. This study confirms the presence of familial risk factors for iritis independent of those governing susceptibility to AS. Association studies have suggested the presence of non-HLA-B27 MHC encoded genetic influences on the risk of developing iritis, including HLA-DR8[11] and the *LMP2* gene[12]. The finding of familiality of juvenile onset of AS confirms that the age of onset of AS is heritable[10]. Age of symptom onset has been associated with carriage of HLA-B27[13] and HLA-DR8[14,15]. The significance levels of these reports have not been very strong, and the findings may represent true association or linkage disequilibrium with other MHC loci. There is a significant need for a systematic study of susceptibility loci both within the MHC and elsewhere to define the genes affecting these traits.

Recent findings provide evidence for the existence of severity genes and identify where in the genome they may lie[7]. Our data reveal that although severity is highly genetically determined, the correlation between family members was not strong enough to be clinically useful in predicting disease outcome. The proportion of variation in disease activity that could be accounted for by the disease activity of the affected sibling was only 7%. Questionnaire based assessment of disease severity is inevitably less objective and more subject to day-to-day variation in completion. Assessment at one point in time was used in this study and perhaps an average of numerous assessments would have given a more stable measure, such as those for BASRI, which is based on cumulative disease. Our study found

significant heritability of radiological change due to AS, and it may prove that BASRI is a more accurate predictor of familiality of disease severity than BASDAI or BASFI.

In summary, severity appears to be determined by genetic and environmental factors. The genetic factors mean that siblings have comparable levels of disease activity of AS, and family members have comparable radiology scores. However, using questionnaire measures of disease severity, the extent of familiality observed was too weak to predict which cases might have a poor prognosis. Iritis and JAS are more likely if there is a parental family history; children of affected AS parents may have a higher risk of developing these conditions.

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