Dutch Patients with Familial and Sporadic Ankylosing Spondylitis Do Not Differ in Disease Phenotype

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ABSTRACT. ***Objective.*** To assess potential differences in the phenotypic expression between familial and sporadic ankylosing spondylitis (AS).

Methods. Clinical data from the patient record forms were compared between 55 patients with AS from multicase families (i.e., families in which ≥ 2 first-degree relatives have the disease) (familial AS) and 110 sex and age matched patients with AS who did not have a first=degree relative with the disease (sporadic AS).

Results. Between familial and sporadic AS no differences were found in age at disease onset, age at diagnosis, or prevalences of peripheral arthritis and acute anterior uveitis.

Conclusion. Potential differences in genetic makeup are not reflected in differences in the phenotypic expression of familial and sporadic AS. (J Rheumatol 2002;29:2583–4)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS DISEASE PHENOTYPE MULTICASE FAMILIES

Ankylosing spondylitis (AS) is a common rheumatic disorder that primarily affects the axial skeleton, and in which peripheral arthritis and acute anterior uveitis are frequent complicating factors. The disease is highly associated with HLA-B27, and among Caucasians over 90% of patients with AS carry this gene[1,2].

Familial aggregation of AS has been known for many years. HLA-B27 positive first-degree relatives of patients with AS have been estimated to have a 10-fold increased risk to develop AS compared with HLA-B27 positive individuals without such family history[3]. This family clustering is largely genetically determined. A recent twin study estimated the heritability in AS to be at least 97%[4]. Since the contribution of HLA-B27 was calculated to be less than 20% and genes linked to the major histocompatibility complex (MHC) as a whole contribute less than 40% to the susceptibility of AS, the disease must be considered multigenic, with complex influences from genes inside as well as outside the MHC region[5].

Little is known about the mode of inheritance and the interplay of these genetic factors that determine AS to aggregate in some families and not others, or about the potential influences they have on disease phenotype in familial versus sporadic AS.

We investigated potential differences in disease phenotype between AS patients from multicase families (i.e., families in which ≥ 2 first-degree relatives have the disease) (familial AS) and AS patients who do not have any first-degree relative with the disease (sporadic AS).

MATERIALS AND METHODS

A questionnaire focusing on family history was sent to all 651 patients with AS registered in our outpatient clinic for rheumatology and rehabilitation. The diagnosis of AS, according to the Modified New York Criteria[6], was confirmed by a rheumatologist in all cases. Patients who answered to have one or more first-degree relatives (father, mother, brother, sister, son, daughter) being treated by a rheumatologist for AS were considered to have familial AS. Patients were considered to have sporadic AS when they denied having first-degree relatives with complaints pointing to AS. Demographic data and clinical characteristics of the responders were gathered from patient record forms.

Every subject with familial AS was sex and age matched (within 1 year) with 2 control patients with sporadic AS. Clinical characteristics were compared between the familial group and the sporadic group. Because of matching, quantitative data were analyzed by Kruskal-Wallis test. For qualitative data, the chi-square test or Fisher's exact test were used.

RESULTS

From the 651 AS patients that were approached, 26 had moved to unknown addresses and a total of 387 (62%) responded, of whom 66 were excluded because of a diagnosis of psoriasis, Crohn's disease, or ulcerative colitis. From the remaining 322 cases 66 (20.6%) were familial and 255 (79.4%) sporadic. After matching for age and sex, 55 familial cases and 110 sporadic cases were studied. Demographic and clinical characteristics of the familial and sporadic groups are presented in Table 1.

Because of matching, sex distribution and mean age were the same in the 2 groups; 20% of the individuals were female. No differences were observed between the familial and sporadic group in the prevalence of peripheral arthritis, acute anterior uveitis, or unilateral sacroiliitis. The prevalence of arthritis of hip and shoulder joints was more than

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Submitted January 4, 2002; revision accepted June 6, 2002.

Table 1. Disease characteristics of patients with familial AS (n = 55) and patients with sporadic AS (n = 110).

Characteristics	No. of Trios with Complete Data	Familial AS	Sporadic AS	OR (95% CI)	p
Median current age, yrs IQR	55	50 (38–54)	50 (38–57)		0.96*
HLA–B27 negative, n (%)	40	0 (0.0 %)	2 (2.5 %)		0.55†
Median age at first complaints, yrs (IQR)	39	20 (18–25)	23 (18–27)		0.3*
Median age at actual diagnosis, yrs (IQR)	49	30 (23–36)	29 (25–37)		0.64*
Median disease duration, yrs (IQR)	39	21 (17–29)	20 (13–31)		0.62*
Peripheral arthritis, n (%)	55	20 (36.4 %)	35 (31.8 %)	1.23 (0.62–2.42)	0.56†
Arthritis, hip/shoulder, n (%)	44	4 (9.0 %)	19 (21.6 %)	0.36 (0.12–1.15)	0.07†
Arthritis, knee/elbow/ankle/wrist, n (%)	47	10 (21.3 %)	17 (18.1 %)	1.23 (0.51–2.93)	0.65†
Arthritis, digits, n (%)	47	8 (17.0 %)	8 (8.5 %)	2.21 (0.77–6.31)	0.13†
Acute anterior uveitis, n (%)	44	16 (36.4 %)	29 (33.0 %)	1.16 (0.55–2.48)	0.70†
Unilateral sacroiliitis, n (%)	51	0 (0.0%)	3 (2.9 %)		0.55†

* Kruskal-Wallis test; † chi-square test/Fisher's exact test. IQR: interquartile range.

twice as high in sporadic cases, but this difference failed to reach statistical significance. No differences were observed between the familial group and sporadic group with respect to age at first complaint, age at actual diagnosis, and disease duration.

DISCUSSION

This study could not demonstrate any difference between familial AS and sporadic AS with respect to age at disease onset, age at diagnosis, or prevalences of peripheral arthritis and acute anterior uveitis. To our knowledge, only one other study focusing on the differences between familial and sporadic AS has been published. In this earlier report, data on the prevalence of peripheral arthritis are lacking, but results concerning age at disease onset and prevalence of acute anterior uveitis are equivalent to our findings[7].

Roughly 20% of our population were familial cases. This percentage is in accordance with earlier findings of 15–20% familial AS cases in British studies[8,9]. Therefore, it is unlikely that the low response rate of 62% biased our study, since the responders are equally divided among familial and sporadic cases. Further, it is unlikely that phenotypic expression of AS influenced the response rate of familial and sporadic cases in a different manner. Due to ethical limitations, we had to rely on patient information about the occurrence of AS within their families. Potentially this could have led to misdiagnosis. However, most AS patients are correct in their statements, as shown[10].

This study focused solely on possible differences in phenotypic expression of AS between familial and sporadic cases. The results indicate that potential differences in genetic makeup between these groups are not reflected in differences in the phenotypic expression.

Recently, it was demonstrated that disease severity in AS is largely genetically determined[11]. Since a more severe disease status in sporadic cases has been documented[7], further research into the potential (genetic) differences between familial and sporadic AS is necessary for prognostic reasons.

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