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The Frequency of Rheumatoid Arthritis among Relatives of Probands with Definite Ankylosing Spondylitis

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We studied families of 23 unrelated HLA-B27 positive probands with definite ankylosing spondylitis to investigate the occurrence of rheumatoid arthritis. The prevalence of RA among these relatives was significant higher (2.91%; $0.02<p<0.05$) than in the control group of 28 healthy individuals (1.02%). These data suggest an increased relative risk of RA in relatives of patients with AS.

Key words: family study, rheumatoid arthritis, ankylosing spondylitis.

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Family studies have previously shown that there is an increased prevalence of ankylosing spondylitis (AS) among relatives of AS patients (1). Further, we know that HLA-B27-positive relatives of AS patients possessing this antigen are more likely to develop AS than HLA-B27-positive relatives of healthy HLA-B27-positive subjects (1). The prevalence of AS seems to be comparable to the rheumatoid arthritis (RA) figure viz. 0.5–1.0% (1, 2).

Similarly, it has been demonstrated that RA occurs more frequently in first-degree relatives of probands with seropositive RA (2, 3). In some cases the rheumatic diagnosis is AS and RA simultaneously in one and the same patient (4–7). On the assumption that these two disorders occur completely independently of each other, simultaneous coexistence in the same patient should occur once in every 50000 to 200000 of the adult population (2, 4–7). However, we have no knowledge of that these two disorders, do in fact, occur independently of each other. In the present study we investigated the frequency of cases with RA in first and second degrees relatives of probands with definite HLA-B27-positive AS.

MATERIALS AND METHODS

For our family study we collected data of all 42 unrelated patients with ankylosing spondylitis seen in the out-patient clinic and hospitalized in the Department of Rheumatology, Kong Christian X Gigthospital, between July 1985 and February 1986. Eleven patients were excluded because they did not meet the inclusion criteria. These criteria were definite AS (4 patients excluded), positive for HLA-B27 antigen (2 patients were negative for this antigen), all younger than 65 years (4 patients) and no history of adoption (1 patient). The 31 patients selected for participation fulfilled all criteria. After receiving the questionnaire, 5 patients felt that they could not answer the questions adequately and 3 patients did not wish to participate.

The clinical diagnosis of AS was based on the New York criteria (1). All 23 probands fulfilled 2 of the 3 clinical criteria, in addition to the radiological criterion of at least grade II bilateral sacro-iliitis. HLA-B27 typing was performed only in the probands' material; none of the relatives were HLA-typed.

All 23 participating AS probands were asked both in writing and at interview regarding their knowledge of cases of RA and AS in their consanguineous family. We defined family as comprising 1) grandparents, 2) parents and their siblings, 3) proband's siblings, and 4) proband's children. Furthermore we asked for name, date of birth and details of hospital admissions of the stated relatives with rheumatic disorders. In each case we confirmed the information given by the probands. We felt

Table I. *Survey of cases of rheumatoid arthritis and ankylosing spondylitis among relatives of probands with definite HLA-B27 positive ankylosing spondylitis*

No.	Sex	Age	Periph. joint erosions	Rheumatoid arthritis	Sero-pos.	Ero-sive	Ankyl. spond.	Rela-tives *n*
1	M	40		Grandmother (maternal)	+	+		19
2	M	49		Grandmother (paternal)	?	+		15
3	M	51	Yes	Father	?	+		19
4	M	47	Yes	Aunt (paternal)	+	+		22
5	M	32		Grandmother (maternal)	+	+		16
				Uncle (maternal)	−	+		
6	F	46		Grandmother (maternal)	+	+	Father	17
				Aunt (maternal)	−	+		
7	M	30		Grandfather (maternal)	?	+		14
8	M	37		Uncle (maternal)	+	+		24
9	F	43		Brother	+	+		25
10	M	33		Uncle (maternal)	+	+		19
11	F	31						12
12	M	48						16
13	F	50						17
14	M	58						15
15	M	45					Borther	21
16	M	27						20
17	M	50						16
18	M	44						20
19	M	25					Father	14
20	M	47						18
21	M	41						13
22	M	47					Brother	20
23	M	55	Yes					21

convinced, only when there existed a hospital case record of the relative, which could prove the rheumatic disease. All RA relatives met the American Rheumatism Association criteria of 'definite' or 'classic' RA.

The control group consisted of 28 healthy volunteers on the hospital staff. None of the control subjects had a history of rheumatic disorders or had been HLA typed. All controls completed the same questionnaire and their data were subjected to the same thorough check-up.

Statistical analysis was calculated by the χ^2-test.

RESULTS

Table I shows a survey of the 23 HLA-B27-positive AS probands, the numbers of their relatives and those among them who had been affected by RA. The total number of first and second degrees relatives in this group was 413. The control group comprised 28 healthy volunteers with 492 relatives.

Based on the questionnaires returned, 15 probands (65%) reported a knowledge of cases of RA among their relatives. In the control group, 4 subjects (14%) gave this information. Our research, based on the hospital case records, could certify the statements given by 10 probands. In 2 cases we could not find any case sheets for the relatives (probands 16 and 23).

Furthermore, 3 of the 15 probands reported on cases of RA among their relatives who were not included among the family members under investigation. Thus proband no. 11

submitted 2 cases: grandmother's (maternal) two sisters; proband no. 12: mother's cousin (female); and proband no. 13: cousin (female) (maternal). All these had documented seropositive, erosive RA.

In the control group one of the 4 subjects' statements could not be confirmed by us, because of a missing case sheet. The other 3 subjects had relatives with verified RA. In this case, one had 1 first-degree and 2 second-degree relatives with RA and the other 2 each had 1 second-degree relative. Thus 4 RA relatives were seropositive, one was seronegative and all had erosions on X-ray.

Thus, 43% of our probands had relatives with RA in their family. According to Table I, 10 second-degree relatives had RA, while only 2 first-degree relatives had the disease. In the control group the RA frequency was only 11%. The prevalence of RA in the probands' relatives material was 2.91% (12:413) and in the control subject group, 1.02% (5:492), $0.02<p<0.05$ ($\chi^2=4.35$).

As shown on Table I, there were 4 first-degree relatives with AS and none in the control group. Further, according to the AS probands, we found peripheral joint erosions in 3 probands, whereas the other 20 probands did not show any peripheral joint involvement.

DISCUSSION

Ankylosing spondylitis and rheumatoid arthritis are in many respects very different disorders. Patients with AS are seronegative for rheumatoid factors and without findings of hypergammaglobulinemia and antinuclear antibodies (1, 2). Although the histologic picture in AS is that of a chronic proliferative synovitis with the presence of mononuclear cells in acutely involved tissue very similar to that of RA, the end-stage characteristic in AS is an enthesopathy rather than erosive joint destruction as seen in RA (1). In fact, there are no real data to support an autoimmune pathogenetic mechanism in AS. However, others have reported that one-third (8) to one-half (6) of AS patients, especially females (1), had peripheral arthritis very similar to that of RA at some stage of the disease.

Therefore, the purpose of the present study was to determine the frequency of RA among relatives of AS probands. Further, to investigate whether there is any relation between peripheral arthritis involvement in AS probands and the occurrence of RA in their relatives, respectively. In addition, previous to this study we knew of 2 cases of AS probands with RA among their first and second degrees relatives. These were neither documented nor included in our study.

According to Table I, our data show that 43% of AS probands had relatives (2 first-degree and 10 second-degree) with well documented RA, whereas the figure only was 11% in the control group. The prevalence of RA was 2.91% in the probands' relatives group and 1.02% in the control group. The significance is calculated by $\chi^2=4.35$ ($0.02<p<0.05$). It is not obvious why there were far more second-degree relatives with RA compared with first-degrees.

Actually, the frequency of RA cases among relatives of AS probands is assumed to be higher. Thus, several probands could report only on part of their family members with respect to the occurrence of rheumatic disease. The figure for AS relatives may illustrate this problem, as all relatives with AS were first-degree male relatives, which may indicate an under-reporting of AS in second-degree relatives and in females. In addition, RA in relatives of 2 probands could not be documented because of missing hospital case records and 3 other probands reported on RA in their relatives who were not included in the defined family. In the control group only one case of RA could not be verified.

All RA relatives of AS probands were erosive, 7 were seropositive and 2 negative for rheumatoid factor. In 3 cases the rheuma-factor determination could not be performed,

because these patients died before this test was introduced. In the control group one RA relative was seronegative and the other 4 were seropositive.

These data show that our knowledge of the epidemiologic mechanism in RA and AS is still incomplete. Our results suggest that RA and AS may share at least one common factor, whether genetic or environmental, which is of importance in the expression of these disorders. This may be supported by the observation that the peripheral arthritis (PA) seen in RA and some cases of AS are very similar. Thus Miehle et al. (9) showed that AS patients positive for HLA-DR4, which is associated with RA, have a 7-fold relative risk of developing a peripheral arthritis. If we assume that AS and RA share common gene(s) for peripheral joint involvement, then we would expect an increased frequency of AS patients with PA among those with RA relatives. Our data fail to show such a relation. Thus, only 20% of AS probands with RA relatives had peripheral joint erosions, compared with 8% in the group of AS probands without RA relatives.

In contrast, we do not know what the number of AS probands with peripheral joint involvement would have been, if all RA relatives had been first-degree. To draw conclusions, we would need HLA-DR4 typing of the AS probands and HLA typing of the relatives, which was not possible.

Our suggestion of one or more common factors between AS and RA is also supported by the observation that patients with seropositive nodular erosive RA may have bony fusion of the peripheral joints, the cervical spine and sacro-iliac joints that is radiologically indistinguishable from that of AS (6, 10).

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