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HLA-DR4 in ankylosing spondylitis with different patterns of joint involvement

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SUMMARY Fifty patients with ankylosing spondylitis (AS) confined to the spine and sacroiliac joints were compared with 50 cases of AS complicated by various patterns of non-axial joint involvement. Radiological and clinical features were evaluated and HLA-DR4 typing was carried out. This antigen was found in 16% of 200 normal individuals in 18% of patients suffering from exclusively axial AS, and in 54% of patients with additional purely peripheral joint involvement (wrist, finger, ankle, toe). The possibility that HLA-DR4 represents a non-specific marker for peripheral arthritis in patients with ankylosing spondylitis is discussed.

Key-words: non-axial joint involvement, non-specific marker, rheumatoid arthritis, ankylosing spondylitis, tissue typing.

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the locomotor system which may involve other systems. The disease progresses at a varying rate, is incurable, and may become inactive at any point in its course.

Non-axial joints are involved in 18 to 75% of cases of AS[1 2] mainly in young patients. Such cases are often diagnosed only retrospectively as AS with the aid of tests for HLA-B27. Arthralgias or arthritides generally begin in one or only a few joints, are frequently transient, and represent in 10–20% of cases the prodromal signs of spinal disease. The joints most commonly affected, with a frequency of up to 40%, are the hips and shoulders.[3] In contrast, disease affecting only the peripheral joints (ankle, toe, hand, and finger joints) is considerably rarer, being described in some 8–14% of cases.

The role of HLA-B27 in the diagnosis, risk assessment, and aetiology of AS is well known. With a disease prevalence of 0·05%, only 0·75% of randomly investigated individuals found to be positive for HLA-B27 later develop AS. Assuming a prevalence of 1% increases this figure to 15%, but even here 85 out of each 100 HLA-B27 positive persons remain 'free of AS.' In contrast to the finding of HLA-B27 positivity, a negative finding has great diagnostic relevance. The likelihood of an HLA-B27 negative individual developing AS is only 0,1%.[4]

An increased occurrence of AS is found neither for other antigens of the B locus nor for those of the loci for A (with the exception of HLA-A2, which shows a linkage disequilibrium with B27), C, D, or DR.

Peripheral arthritis (PA) in AS, defined as affecting only ankle, toe, hand, and finger joints, is often indistinguishable radiomorphologically and histologically from rheumatoid arthritis (RA). In this context the emergence over the last few years of a correlation between RA and HLA-DR4 in some 50–60% of cases prompted us to examine the frequency of HLA-DR4 in AS with and without involvement of various joints outside the axial skeleton.

Patients and methods

The study was carried out at the Klinik Wendelstein, Rheumazentrum der BfA, 8202 Bad Aibling, West Germany, between May 1982 and October 1983. Included in the study were 50 patients with AS restricted to the axial skeleton (typical changes in the sacroiliac joints and spine) and 50 patients with

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Table 1 *Diagnostic criteria for ankylosing spondylitis*[5]

Clinical criteria
(1) Deep lumbar pain and stiffness for more than 3 months not improved by rest
(2) Pain and stiffness in thoracic region
(3) Limitation of mobility in lumbar spine
(4) Limited expansibility of rib cage (respiratory movement)
(5) History or objective evidence of iritis or its sequelae

X-ray criteria
Radiologically shown bilateral changes of sacroiliac joints characteristic of ankylosing spondylitis (not arthrosis!).

Table 2 *Standardised radiographic evaluation of arthritides*[6]

Grade 0: Normal joints
Grade 1: Slight abnormality
One or more of the following lesions must be present:
soft tissue swelling
periarticular osteoporosis
slight joint space narrowing
These criteria should always be substantiated by comparison with a healthy contralateral joint or with an earlier film of the same joint
Grade 2: Definite early abnormality
Erosion and moderate joint space narrowing.
Erosion is obligatory except in the weight-bearing joints.
Grade 3: Medium destructive abnormality
Erosion and marked joint space narrowing.
Grade 4: Severe destructive abnormality
Erosion, severe joint space narrowing.
Bone deformation in weight-bearing joints.
Grade 5: Mutilating abnormality

AS complicated by non-axial joint involvement of varying kinds. Various clinical, radiological, and laboratory investigations were carried out, and the presence or absence of HLA-DR4 was ascertained in each patient.

The diagnosis of ankylosing spondylitis was established according to Kellgren's criteria[5] (Table 1). We excluded cases of AS which had begun in childhood, all other seronegative spondylarthritides, and all chronic or acute polyarthritides without the axial involvement typical of AS. Peripheral joint involvement, defined as affecting only ankle, toe, hand, and finger joints, was established by the history (swelling, pain, effusion), clinical manifestations (synovitis, effusion) and, above all, by *x*-ray criteria[6] (Table 2). A history of peripheral joint pain or inflammation not substantiated by objective evidence was not considered to be proof of peripheral joint involvement.

Tissue typing was carried out in the National Reference Laboratory (Professor Dr D. Albert), Universitätspolikinderklinik, Pettenkoferstr. 20, 8000 München, West Germany. HLA-B27 was determined by a standardised lymphocyte toxicity test and HLA-DR4 with the aid of B cell preparations. The results obtained were compared by means of the χ^2 test with the Yates's correction. Relative risk (RR) was calculated with the formula: $RR=(P+)\times(C-)/(P-)\times(C+)$, where P+ and P− are the number of patients and C+ and C− the number of controls positive and negative for HLA-DR4 respectively.

Table 3 *Age and sex distribution of investigated cases of AS*

Patient group	*Number*	*Mean age*	*Men:women*
Axial AS	50	43 years	4·5 : 1
AS with non-axial joint involvement	50	41·5 years	3·5 : 1

Table 4 *Different forms of non-axial joint involvement in the investigated cases of AS*

Patient group	*Number of cases*
AS with non-axial joint involvement	50
AS with purely peripheral involvement (ankle, toe, hand, finger joints)	13
AS with involvement of peripheral joints + elbow/knee	15
AS with involvement of peripheral joints, elbow/knee + hip/shoulder	22

Table 5 *HLA-DR4 and HLA-B27 in AS with and without various forms of non-axial joint involvement*

Patient group	*Number*	*HLA-B27+ %*	*Number*	*HLA-DR4+ %*
Control group	—	4–10*	200	16
Purely axial AS	50	94	50	18
AS with and without non-axial joint involvement	100	94	100	25
AS with non-axial joint involvement	50	94	50	32
AS with exclusively peripheral joint involvement	13	92·3	13	54

*Kelsey.[8]

Table 6 *Nature of peripheral joint involvement, HLA-DR4, peripheral and axial x-ray findings, history, and clinical findings in the 13 patients with pure peripheral arthritis*

Serial number	*Age (yr), Sex*	*X-ray findings in SI joints and spine*	*Peripheral joint involvement: (a) History (b) Clinical findings (c) X-ray*	*Radiographic classification of peripheral arthritis according to Larsen et al.[6] Stages 0–5*	*HLA-DR4 +/−*
1	44, M	Ankylosis of SIJ, syndesmophytes	a+b+c: right forefoot c: right MTP joints II, III: erosions, subluxations	2	+
2	39, M	Ankylosis of SIJ, syndesmophytes spondylarthritis, diskitis	a+b+c: left ankle c: increased isotope uptake	0	+
3	41, M	Bilateral sacroiliitis, syndesmophytes, vertebral squaring, spondylarthritis	a+b+c(c): right MCP joints II, III c: Above all, interruption of articular cortex in right MCP joint II	1	+
4	41, M	Bilateral sacroiliitis, post-inflammatory fusion of cervical spine, enthesitis in C5/C6	a+c: bilateral MTP joints V; c: narrowing of joint space, osteoporosis, interruption of articular cortex	1	−
5	42, M	Florid bilateral sacroiliitis, syndesmophytes, spondylarthritis	a+b+c: right MTP joints II–V; c: right MTP joint II: erosion, narrowing of joint space	2	+
6	36, M	Florid bilateral sacroillitis*	a+b+c: left MTP joints III, IV; c: narrowing of joint space, erosion, pseudocyst	2	+
7	39, M	Ankylosis of SIJ, syndesmophytes, ventral atlantoaxial dislocation	a+b+c: right MTP joints II–V; c: osteoporosis, erosion, luxation	3	−
8	45, F	Florid bilateral sacroiliitis*	a+b: marked synovitis in region of right wrist; marked limitation of movement c: −	0	+
9	50, F	Bilateral sacroiliitis, vertebral squaring, syndesmophytes, spondylarthritis	a+b+c: left ankle c: osteoporosis, pseudocyst	1	+
10	30, F	Florid sacroiliitis*	a+b+c: right MTP joints II–V, left MTP joints III, IV c: erosion, narrowing of joint space, subluxation	3	−
11	57, M	Ankylosis of SIJ, syndesmophytes, spondylarthritis. Above all, diskitis	a+b+c: left wrist c: osteoporosis, narrowing of joint space	1	−
12	19, F	Florid bilateral sacroiliitis*	a+b+c: right MTP joint II c: pseudocyst, interruption of articular cortex	2	−
13	44, M	Bilateral sacroiliitis, spondylarthritis, costovertebral arthritis, vertebral squaring	a+b+c: forefoot c: osteoporosis, pseudocyst, erosion, mutilation	4	−

*The diagnosis of these cases of AS was confirmed by additional clinical and anamnestic criteria (e.g., heel pain, iritis, morning lumbar pain).

Table 7 *HLA-DR4 in AS with various forms of non-axial joint involvement*

Patient group	*Number*	*HLA-DR4 positive (%)*
Control group	200	16
Peripheral joint involvement + elbows/knees	15	26.6
Exclusively peripheral joint involvement	13	54

Table 8 *'Rheumatoid factor' and family history in various courses of AS*

Patient group	*Number*	*Demonstration of RF (latex fixation test and/or SCAT) (%)*	*Family history of AS (%)*
AS with no non-axial joint involvement	50	2	12
AS with non-axial joint involvement	50	10	10
AS with exclusively peripheral joint involvement	13	0	14

'Rheumatoid factor' positive in 4–8% of control group.
Family history of AS according to literature in approximately 6%.[15]

Results

A profile of the patients in terms of age and sex is given in Table 3. Of particular interest in this study were the 50 patients with non-axial joint involvement. In Table 4 this group is subdivided into those with peripheral arthritis, those with PA and additional involvement of the knees or elbows, and finally those with in addition involvement of shoulders or hips. The occurrence of HLA-B27 and HLA-DR4 in the various groups is shown in Table 5. Peripheral and axial radiological findings are given for the individual patients with purely PA in Table 6, together with their HLA-DR4 status.

For each of the disease patterns described above we determined HLA-DR4 frequencies, as shown in Table 7.

We attempted to establish correlations between AS with varying joint involvement and a family history of AS, the presence of 'rheumatoid factor,' and the combination of HLA-DR4 and HLA-B27, as well as between HLA-DR4 positivity and the severity of the radiological changes.

In Table 8 the patients with PA are analysed with respect to the presence of 'rheumatoid factor' and a family history of AS.

There exists no linkage disequilibrium between HLA-DR4 and HLA-B27 which might modify the percentage frequencies of HLA-DR4 in our subgroups. The differences between the control group and, on the one hand, the patients with AS restricted to the spine (n=50) and, on the other hand, those with PA were not significant. Comparison between the relative frequency of HLA-DR4 in those AS patients with no non-axial joint involvement and in patients with PA gave $\chi^2 = 7{\cdot}8$, $p=0{\cdot}005$. Comparison between AS with PA and the group with additional involvement of knees, elbows, hips, and shoulders gave $\chi^2 = 5{\cdot}5$, $p=0{\cdot}002$ (with Yates's correction).

AS patients positive for HLA-DR4 were calculated to have a 7-fold relative risk of developing a

Table 9 *HLA-DR4 in rheumatoid arthritis*

Authors	*Control group (%)*	*Number of cases of (n)*	*Seropositive + seronegative RA (%)*	*Seronegative RA (%)*	*Seropositive RA (%)*
Dubloug *et al.*[16]	27	48	50	27	61
Sakurami *et al.*[17]	33	50	56	33	59
Swiss Coll.[18]	19	132	44	23	50
Queiros *et al.*[19]	12	80	49	39	90
Alarcón *et al.*[20]	14	130	44	27	56
Scherak *et al.*[9]	21	111	54	42	57
Total/average	21	551	49.5	32	62

purely PA. This risk was similar to that of an HLA-DR4 positive individual developing rheumatoid arthritis.

Our investigations showed no correlations between HLA-DR4 and HLA-B27 positivity or negativity, between HLA-DR4 and a family history of AS, nor between HLA-DR4 and the presence of 'rheumatoid factor.'

Discussion

The type of AS with additional involvement of only the peripheral joints was formerly described as the 'Scandinavian form' and sometimes thought of as being intermediate between AS and seronegative RA. The term 'Scandinavian form' has today been abandoned. Moreover, it is now accepted that the occurrence of both diseases in one person is extremely rare, only some 30 cases of true coexistence between RA and AS having been reported.[7] The prevalence of peripheral arthritis in our series of AS patients is consistent with that generally reported. The nature of the joint involvement differs from the symmetrical and ordinarily polyarthritic pattern typical of RA. Here an asymmetrical and mono- or pauciarticular pattern is normally seen. However, inability to distinguish between the two diseases on the basis of *x*-ray appearance or synovial membrane histology led, as late as the middle of 1950s, to use in America of the term 'rheumatoid spondylitis'–conceived of as being a variant of rheumatoid arthritis.

In adult rheumatoid arthritis the HLA-DR4 antigen is much more common than in healthy reference populations. The risk of an HLA-DR4 positive individual developing rheumatoid arthritis is six times greater than for someone not possessing this antigen.[8] HLA-DR4 correlates most strongly with seropositive forms of the disease (Table 9). Several recent publications have, however, found no difference between the occurrence of HLA-DR4 in seropositive and seronegative rheumatoid arthritis.[9] The HLA-DR4 gene locus probably lies in close proximity to genetic structures which regulate the immune response and are thus capable of inducing certain pathological reactions. By further genetic analyses it may be possible in the future to find differences between seronegative and seropositive rheumatoid arthritis and thus to create new areas of definition for subgroups of the entity 'adult RA.'[10]

So far no association between ankylosing spondylitis and HLA-DR4 has been established.[12 13] In 1983 Armstrong and coworkers[14] investigated 33 patients with AS for the presence of HLA-DR4 and other antigens. In 15 patients without peripheral arthritis and 18 patients with peripheral arthritis (including hip or shoulder involvement) HLA-DR4 was found with a frequency of 33·3 and 22·2% respectively, as opposed to 33·8% in the healthy controls.

In contrast to these findings the occurrence of HLA-DR4 in our patients with purely peripheral joint involvement (ankle, toe, finger, wrist) was, at 54%, comparable with the frequency in seropositive rheumatoid arthritis, and markedly higher than in the control group (16%). Comparison between the occurrence of HLA-DR4 in exclusively axial AS and patients with peripheral joint involvement gives $\chi^2 = 7{\cdot}8$ ($p=0{\cdot}005$). Comparison of AS with PA and the group with manifestations in the knees, elbows, hips, and shoulders gives $\chi^2=5{\cdot}5$ ($p=0{\cdot}02$).

From our results it can be calculated that AS patients positive for HLA-DR4 have a 7-fold relative risk of developing a peripheral arthritis. This distribution of HLA-DR4 between the various subgroups raises the following questions:

(1) Is HLA-DR4 a non-specific marker for peripheral arthritides which codes for peripheral joint involvement in the context of ankylosing spondylitis?

(2) Is the risk of peripheral joint involvement in HLA-DR4 positive AS patients higher than in DR4 negative patients?

(3) Is AS with peripheral joint involvement in fact a separate disease entity, despite being indistinguishable on the basis of *x*-ray appearance and synovial membrane histology?

Further investigations, with greater numbers of cases, are needed to provide a clear answer to these questions.

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