POSSIBLE ANKYLOSING SPONDYLITIS IN ACUTE ANTERIOR UVEITIS

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SUMMARY

HLA-B27 typing of 103 acute anterior uveitis (AAU) patients showed that 49 (48%) were positive for this antigen. Of these HLA-B27 positive AAU patients, 27 (55%) had ankylosing spondylitis (AS) according to the New York criteria. The 22 HLA-B27 positive AAU patients without AS, however, also showed symptoms and signs of AS. Seventeen (77%) of these 22 HLA-B27 positive AS negative AAU patients fulfilled a set of criteria for classification as possible AS. In the group of 54 HLA-B27 negative AAU patients, only two patients (4%) had AS. Of the remaining 52 patients only seven (13%) had possible AS. Of the 21 patients having posterior uveitis (PU) none was HLA-B27 positive nor met the criteria for AS or possible AS. These findings indicate a strong relationship between AAU, AS or possible AS and HLA-B27 and suggest that HLA-B27 typing in AAU patients is important for early diagnosis of AS.

KEY WORDS: Acute anterior uveitis, Ankylosing spondylitis, HLA-B27.

EARLY diagnosis of ankylosing spondylitis (AS) is problematic. About 10% of patients with spondylitis do not have sufficient complaints at an early stage of the disease to seek medical treatment (1), and it may take three to ten years before physical and X-ray examination reveal diagnostic abnormalities (2).

Low back pain caused by sacroiliac arthritis is the initial symptom in about 70% of the adult AS patients, whereas acute anterior uveitis (AAU) is one of the first signs in only 1-10% (3). However, during the course of AS the incidence of AAU increases to 20-30% (4).

Both AS and AAU are strongly associated with the HLA-B27 antigen (5). When AAU develops in an AS patient an absolute association (100%) with HLA-B27 (5, 6) is observed. In the present study we attempt to ascertain the importance of HLA-B27 typing in AAU patients, by determining the incidence of AS in HLA-B27 positive and negative patients. Emphasis was placed on the occurrence of signs and symptoms of AS in HLA-B27 positive AAU patients without definite AS. We therefore developed a set of criteria for 'possible AS'.

Our results indicate that rheumatological examination of HLA-B27 positive AAU patients reveals symptoms of AS or possible AS in most of these patients.

PATIENTS AND METHODS

Unselected patients with uveitis were seen by one of the three authors (M.R.D., B.J.C., G.S.B.). The patients were considered to have AAU when the inflammation was confined to the anterior segment of the eye, and to have posterior uveitis (PU) when the inflammation was confined to the posterior segment. Patients with panuveitis were excluded from the study. The HLA-B27 antigen was tested in all patients by the NIH technique (7). Patients with AAU (= 112) and PU (n=21) were examined for AS by one of us (A.L.) without prior knowledge of the results of the HLA-B27 test.

All patients were questioned about their history of lumbar pain, peripheral arthritis and arthralgia, heel pain, gastrointestinal or urogenital complaints, skin or mucosal lesions and possible infectious diseases in the past. Patients with specific diagnosis like sarcoid (n = 3), Behçet's disease (n = 3) and with associated diseases like Reiter's (n = 2) or psoriasis (n = 1) were excluded from the study. The patient sample therefore was confined to 103 cases of endogenous AAU.

Physical examination included measuring the flexion capability of the lumbar spine by the modified technique of Schober (normal shift > 5 cm) (8) and examination of spinal movements in three planes. Chest expansions were determined by a tape measure reading at nipple level in males and below the breasts in females (normal shift > 5 cm).

X-ray assessment of the sacroiliac joint took place in antero-posterior view of the pelvis in a 25° craniocaudal direction. The radiographs of each patient were examined by an experienced rheumatologist (A.J.D.-S.), who had no prior information concerning the clinical and genetic findings.

The diagnosis of AS was made according to the New York (NY) criteria (9). We introduced the term possible AS for those cases not fulfilling the NY criteria but showing subtle clinical and radiologic changes associated with AS. The criteria we used for the diagnosis of possible AS are given in Table I.

TABLE I
CRITERIA FOR 'POSSIBLE AS'

A patient is considered to have possible AS when the New York criteria (9) for AS are not fulfilled and when two of the four following criteria are present:

1. Low back pain and/or peripheral arthritis and/or arthralgia, and/or heel pain.
2. Limitation of lumbar spine movement (Schober shift ≤ 5 cm) and/or chest expansion (≤ 5 cm).
3. Sacroiliitis on X-ray examination: grade II, uni- or bilateral (9).
4. A relative affected with AS.

RESULTS

We studied 103 patients with AAU and 21 patients with PU. The group of AAU patients consisted of 58 males and 45 females. The mean age of the males was 34 years and of the females 45 years. The group of PU patients consisted of 11 males, mean age 35 years, and 10 females, mean age 38 years.

Frequency of AS in HLA-B27 positive and negative patients

AS was found in 29 out of 103 (28%) of the AAU patients. HLA-B27 typing of these 103 AAU patients showed that 49 (48%) patients were positive for this antigen. Of these 49 HLA-B27 positive AAU patients 27 (55%) had AS according to the New York criteria. In the 54 HLA-B27 negative AAU patients, AS was only found in two cases (4%) and this difference is statistically significant ($p < 0.001$). The 21 PU patients did not show HLA-B27 positivity and none of them met the NY criteria for AS.

Frequency of possible AS (Table I) in HLA-B27 positive and negative patients (Table II)

Of the AAU patients, 74 did not have AS, and 22 of these were HLA-B27 positive. Many of these 22 HLA-B27 positive AAU patients nevertheless showed some symptoms of AS. We therefore developed criteria for possible AS (Table I). Of these 22 patients, 17 fulfilled these criteria (Table II).

TABLE II
NUMBER OF POSSIBLE AS CRITERIA IN 74 AAU PATIENTS WITHOUT AS

	Number of criteria fulfilled					Total
	0	1	2	3	4	
HLA-B27+	2	3	9	7	1	22
HLA-B27-	23	22	7	0	0	52
Total	25	25	16	7	1	74

The frequency of the criteria for possible AS in the 22 HLA-B27 positive AAU patients without AS is given in Table III. Of the 52 HLA-B27 negative AAU patients without AS only seven patients met the criteria for possible AS (Table II). The frequency in which these criteria were found is shown in Table IV. Of these seven possible AS patients, six had low back pain. Their ages ranged between 49 and 79 years. Three of these six patients were known to have spondylarthrosis lumbalis.

In Table V the frequency of the possible AS criteria in the group of 21 PU patients is given. None of these patients met more than one criterion for possible AS. In conclusion we may state that possible AS occurs mainly in HLA-B27 positive AAU patients. The incidence of AS and/or possible AS in HLA-B27 positive AAU patients reached 90%, compared to only 17% in the HLA-B27 negative patients (Fig.) ($p < 0.001$).

Sensitivity and specificity of the criteria for possible AS in HLA-B27 positive and negative AAU patients without AS (Table VI)

Evaluation of the criteria for possible AS indicated that having a relative with AS is highly discriminatory for possible AS. Seven of the 74 AAU patients without AS had relatives with AS and all these seven patients were positive for the HLA-B27 antigen. Sacroiliitis as a criterion for possible AS was found in 17 of the 74 patients, 10 of them being HLA-B27 positive. All 10 were considered to have possible AS, compared to seven HLA-B27 negative AAU patients without AS of whom only two were considered to have possible AS. This criterion is therefore less specific but more sensitive.

TABLE III
POSSIBLE AS CRITERIA IN 22 HLA-B27 POSITIVE AAU PATIENTS WITHOUT AS

Number of patients	Low back pain peripheral joint pain, heel pain	Limitation flexion lumbar spine/ chest expansion	SI-itis	Relative with AS
1	+	+	+	+
4	+	+	+	-
2	+	+	-	+
1	+	-	+	+
2	+	+	-	-
3	+	-	+	-
2	+	-	-	+
1	-	+	+	-
1	-	+	-	+
17				
1	+	-	-	-
2	-	+	-	-
2	-	-	-	-
5				
22	16	13	10	7

TABLE IV
POSSIBLE AS CRITERIA IN 52 HLA-B27 NEGATIVE AAU PATIENTS WITHOUT AS

Number of patients	Low back pain peripheral joint pain, heel pain	Limitation flexion lumbar spine/ chest expansion	SI-itis	Relative with AS
5	+	+	-	-
1	+	-	+	-
1	-	+	+	-
7				
12	+	-	-	-
5	-	+	-	-
5	-	-	+	-
23	-	-	-	-
45				
52	18	11	7	0

TABLE V
POSSIBLE AS CRITERIA IN 21 HLA-B27 NEGATIVE PU PATIENTS WITHOUT AS

Number of patients	Low back pain peripheral joint pain, heel pain	Flexion limitation lumbar spine/ chest expansion	SI-itis	Relative with AS
7	+	-	-	-
1	-	-	+	-
13	-	-	-	-

The limitation of lumbar flexion and/or chest expansion was even more sensitive and less specific. In the HLA-B27 positive AAU patients without AS, 13 of 22 patients had these abnormalities at physical examination, of whom 11 were considered to have possible AS compared to 11 of 52 HLA-B27 negative AAU patients without AS of whom six were considered to have possible AS. Low back pain and/or peripheral arthritis and/or arthralgia was the most sensitive but least specific criterion for the diagnosis of possible AS. In the HLA-B27 positive AAU patients without AS 16 of 22 had complaints, of which 15 were considered as possible AS, compared to 18 of 52 HLA-B27 negative AAU patients without AS of whom only six were considered to have possible AS. In conclusion, a relative with AS in the family of an AAU patient, or sacroiliitis on X-ray examination in such an AAU patient, strongly points towards the diagnosis of possible AS. HLA-B27 typing of AAU patients is a useful tool in ascertaining those at risk of having a mild form of AS.

TABLE VI
SENSITIVITY AND SPECIFICITY OF POSSIBLE AS CRITERIA IN 74 AAU PATIENTS WITHOUT AS

Criteria	Sensitivity* %	Specificity† %
1. Low back pain and/or peripheral arthritis and/or arthralgia and/or heel pain	88	74
2. Limitation of lumbar spine movement (Schober shift $\leq$ 5 cm) and/or chest expansion ($\leq$ 5 cm)	71	86
3. Sacroiliitis on X-ray examination: grade II, uni- or bilateral (9)	50	90
4. A relative affected with AS	29	100

*Sensitivity = no. of possible AS patients with AAU fulfilling this criterion/total no. of possible AS patients.

†Specificity = no. of patients with AAU, without possible AS, not fulfilling this criterion/no. of AAU patients without possible AS.

FIGURE—Frequency of ankylosing spondylitis and possible ankylosing spondylitis in patients with acute anterior uveitis.

Sex and age differences in HLA-B27 positive and negative AAU patients with and without AS (Fig.)

The male:female ratio was 32:17 or 1.9:1 in the 49 HLA-B27 positive AAU patients. In the 54 HLA-B27 negative AAU patients, the male:female ratio was 26:28 or 0.9:1. This difference was statistically significant ($p < 0.01$) (Student's t test). The mean age of the AAU patients was 34 in the HLA-B27 positive patients and 42 in the HLA-B27 negative patients respectively and this difference is statistically significant ($p < 0.01$).

The Figure shows that HLA-B27 positive AAU patients are prone to AS or possible AS. When they are young (≤ 40 years of age) 42% have possible AS and 50% AS. Above the age of 40 years only 15% have possible AS, while the frequency of AS increases to 70%. Although this shift is not statistically significant ($0.2 > p > 0.1$) in the χ^2 test, the overall age of the HLA-B27 positive patients with possible AS (mean 28 years) was significantly lower than of those with AS (mean 37 years) (Student's t test $p < 0.02$). Differences between male and female were not observed in this respect.

In the HLA-B27 negative AAU patients 33% of the male patients over 40 years of age had some symptoms of possible AS. None of them had AS according to the New York criteria. Half of these patients were known, however, to have spondylarthrosis lumbalis.

A small proportion of patients in the HLA-B27 negative female group had AS. One female patient with AS was older than 40 years and was known to have rheumatoid arthritis. Half of the possible AS

patients over 40 were known to have spondylarthrosis lumbalis. These observations suggest that most of the HLA-B27 positive AAU patients are prone to develop AS according to NY criteria as they become older, whereas nearly all HLA-B27 negative AAU patients will not develop AS at all.

DISCUSSION

The incidence of AS in the AAU patients in the present study was 28%. Several authors (10–12) reported an incidence of 15–20%. The difference in results is probably due to our systematic search for AS.

The incidence of AS in HLA-B27 positive and negative AAU patients was previously studied by Brewerton and James (13), Russell *et al.* (14), Møller *et al.* (15) and Verbraeken *et al.* (16). They found AS in a total of 49 out of 120 (41%) of HLA-B27 positive AAU patients, compared to a total of five out of 85 (4%) of HLA-B27 negative AAU patients. These figures were confirmed in the present study. We found that 55% of the HLA-B27 positive AAU patients had AS, according to the NY criteria, while only 4% of the HLA-B27 negative AAU patients had AS.

Diagnosis is often difficult in early AS. Several authors (1, 17, 18) have described the clinical symptoms and signs of early AS, which they called 'Pre-AS'. The term Pre-AS suggests that these patients will actually develop AS. Many patients, however, will develop HLA-B27 associated arthropathy without involvement of the sacroiliac joints and/or spine. It could be said that AAU patients with positive HLA-B27 antigen, but without locomotor disease, are monosymptomatic cases of AS (19). We prefer the term 'possible AS' for those patients with some symptoms of AS, but not fulfilling the criteria for definite AS.

With our classification of possible AS (Table I), 17 of the 22 HLA-B27 positive AAU patients without AS met the criteria for possible AS. The mean age of this group was lower than in the HLA-B27 positive AAU patients actually having AS. This might suggest that AS may develop in these patients in the future. Adding these 17 patients with possible AS to the 27 patients actually having AS, 90% of the HLA-B27 positive AAU patients in our study revealed symptoms of this disease.

In our control group of 21 PU patients, no association with HLA-B27 positivity was observed and no patient fulfilled criteria for possible AS.

Evaluation of the criteria for possible AS suggests that a relative with AS in the family and sacroiliitis on radiologic examination are both discriminating criteria. Low back pain and limitation of lumbar flexion and/or chest expansion are less specific, but more sensitive, criteria. As half of the few HLA-B27 negative patients fulfilling the criteria for possible AS manifest other locomotor diseases, we propose HLA-B27 positivity as a fifth criterion in the diagnosis of possible AS in AAU patients. If this is accepted, three criteria should be fulfilled before the diagnosis of possible AS is made. The high frequency of AS in HLA-B27 positive patients and the high incidence of symptoms and signs of possible AS in the HLA-B27 positive AAU patients without AS suggest an eventual development of AS in nearly all HLA-B27 positive AAU patients.

Comparing the AAU patients for their sex ratio, a preponderance of males was observed in HLA-B27 positive AAU patients; this is consistent with the literature (5). In the HLA-B27 negative AAU group, however, the sex ratio was one to one. When AS occurred in HLA-B27 negative AAU patients, it was only in females instead of males.

A different complex of clinical symptoms of AAU was also observed between HLA-B27 positive and negative AAU patients. This observation will be discussed in a future paper. These differences suggest that HLA-B27 negative AAU defines a group of distinct diseases.

The clinical implications of the study presented here seem to be evident: HLA-B27 typing is of great importance in AAU-patients. The majority of these patients reveal symptoms of AS or possible AS leading to an early diagnosis, which may prevent disability in these patients when treated adequately at this stage of their disease.

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DISCUSSION

Woodrow: Patients who have ulcerative colitis and who are B27 positive have a much higher risk of developing sacroiliitis and ankylosing spondylitis than a random B27 positive population. We do not believe that this is due to the colitis producing spondylitis, since it is usually interpreted in genetic terms. If you have the genes for 'inflammatory bowel disease', plus B27, you have an increased risk of developing AS. The frequency of AS-like disease in your B27 positive uveitis patients is very high and far higher than in a random B27 positive population.

There are two possible explanations: either there are 'spinal' B27 positive individuals—the kind we rheumatologists are looking for—in the B27 population, or the other possibility is that, having had uveitis, they are much more likely to develop spondylitis because they have been exposed to the same aetiological agent. Which possibility would you favour?

Feltkamp: It is a difficult question to answer, because we have not studied random B27 populations for either uveitis or AS.

Woodrow: Why is there so much spinal disease in the B27 positive uveitis patients? You quoted a figure of 90%, which is a much higher figure than when compared to a random population of B27 individuals? There is something odd about these patients with uveitis.

Feltkamp: I don't think our studies, so far, can clearly distinguish between these possibilities until we have studied random B27 populations.

Calabro: I saw something encouraging in your figures, something that we have been seeing for a long time. The actual presence of HLA-B27 helped you in your assessment of outcome for long-term vision. When you look at children with juvenile polyarthritis who develop chronic iridocyclitis, they have all the bad features similar to your B27 negative uveitis patients: they develop cataracts, glaucoma and band keratopathy. So, in fact, nobody lost vision if they had anterior uveitis and possessed B27: maybe B27 is protective.

The chronic iridocyclitis group intrigues me. You mean all those complications occurred, even after you took out all the patients who had chronic iridocyclitis for six months or more?

Feltkamp: Yes.

Khan: What we have heard, is a very nice analysis of acute anterior uveitis in AS patients. It has been clearly demonstrated in this study that there is genetic as well as clinical heterogeneity in acute anterior uveitis. I would like to suggest that the next step would be to study acute anterior uveitis in Reiter's syndrome and other related arthropathies. In some of our studies, acute anterior uveitis is much more severe in patients with Reiter's syndrome. I know of three Reiter's syndrome patients who have lost vision in one or both eyes from chronic recurrent anterior uveitis. Some of these patients had pan-ophthalmitis and I have not yet seen such severe disease in AS patients who had uveitis.

Feltkamp: Were all these Reiter's patients B27 positive?

Khan: Yes.

Møller: Our results, in general agree with yours, but we were reluctant to include back pain and arthralgia, because in our studies these did not correlate well with clinical signs.

Feltkamp: I agree that 'back pain' is one of the weakest criterions in our study, because nearly 50% of normal individuals complain of backache. The most positive criterion was a relative with AS, which is not surprising.

Kåss: We have similar results in our Norwegian studies. However, since we are in England, we must not forget that Scott said some 40 years ago that the prespondylitic phase of the disease was a distinct entity.