Sacroiliitis and HLA. A clinical and genetical study

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SUMMARY Among 39 patients (23 males, 16 females) with sacroiliitis (SI) 17 were HLA-B27 positive. The female/male ratio in the B27-positive group was 2/15. Seventy-four first-degree relatives of 26 probands were also investigated. A high occurrence of SI (20%) was observed in the families of B27-positive probands compared with only 3.7% in the families of B27-negative probands. In the former families SI occurred only in B27-positive subjects with an earlier onset of symptoms and a male prevalence. In the latter, the disease showed a later onset and a lack of male preponderance. The nosological and prognostic relevance of the B27 typing is stressed.

The inflammatory involvement of sacroiliac joints is one of the first and constant signs of classical ankylosing spondylitis (AS). This strong association has been so widely confirmed that the presence of sacroiliitis (SI) is an essential requirement for AS diagnosis according to the 'New York criteria' (Gofton, 1968). It is also well known that SI may be found in patients without any further tendency to spinal involvement.

The nosological distinction between AS and SI is not well established. However, some epidemiological and clinical findings show that the two diseases display in part different behaviours: (a) the prevalence of SI in the population is estimated by the majority of authors to be about one order of magnitude higher than that of AS (1-3% versus 0.2%; but see Kidd *et al.*, 1977); (b) the sex ratio does not show the established higher proportion of males found among AS probands; (c) the association with the HLA-B27 antigen differs in the two diseases, being about 90% in AS and significantly lower in SI.

Family studies carried out on AS together with HLA typing have already shown the high familiarity and the major role played by the B27 antigen in the susceptibility to the disease: about 22% of the first-degree relatives were affected, all of them carried the B27 antigen. On the basis of these results it was concluded that susceptibility to AS is controlled by a

major gene, dominant and linked to HLA with a penetrance of about 30-40% (Contu *et al.*, 1977; Daneo *et al.*, 1977; Kidd *et al.*, 1977).

Following the same approach it was decided to carry out a family study on SI. The results show that it is possible to recognise among SI patients two distinct clinical entities with different genetic and prognostic patterns.

Patients and methods

Patients

Thirty-nine probands (or primary cases) were selected among those patients who had been attending the Rheumatological Centre (San Giovanni Hospital, Torino) during the last 10 years, and who had been diagnosed as having SI. In order to obtain a more homogeneous sample, those patients showing associated diseases (psoriasis, ulcerative colitis, Crohn's disease, and Reiter's syndrome) were excluded. A total of 74 first-degree relatives of the probands were examined. All probands and their relatives (over the age of 15 years) were HLA typed and submitted to careful pelvic x-ray examination. Furthermore, they were investigated for signs and symptoms related to the axial and peripheral musculo-skeletal system. Cardiovascular, respiratory, gastrointestinal, skin, and neurological functions were also checked.

To assess the SI prevalence in our 'normal' population from an unbiased sample, 213 pelvic x-ray films of patients with urological complaints were chosen at random from the records of the Department of Urology and examined for SI with the same criteria as given below. Pathological signs of SI were found in 1.87% of the subjects

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with no significant sex difference (2/101 males; 2/112 females).

DIAGNOSTIC CRITERIA

In probands and in relatives a diagnosis of SI was established when the two following conditions were fulfilled.

(1) Definite radiological involvement of the sacroiliac joints, either at one or both sides, according to Gofton (1968): 0=normal; 1=doubtful; 2=unequivocal sacroiliitis, characterised mostly by marginal sclerosis with minimal erosions without clear alteration of the joint width; 3=preponderance of erosions, widening, and narrowing of the joint width with partial ankylosis; 4=total ankylosis. The scores were assigned blindly and independently by a rheumatologist and a radiologist. In the case of discordance the lower score was assigned. A definite diagnosis of SI was made in the presence of a score of 2 or more, at one or both sides. Individuals showing doubtful signs were considered to be normal.

(2) Absence of signs and symptoms that should justify a diagnosis of AS, either probable or definite, according to the so called 'New York criteria' (Gofton, 1968).

HLA TYPING

Probands and relatives, of a total of 113 individuals, were typed by the standard NIH lymphocytotoxicity technique (Ray *et al.*, 1976) for the following HLA-A, B, and C locus specificities: A1, 2, 3, 9 (w23, w24), 10 (25, 26), 11, 28, w19 (29, w30, w31, w32, w33); B5 (w51, w52, w53), 7, 8, 12 (w44, w45), 13, 14, 15 (To52, To53), 17, 18, w21 (w49, w50), w22, 27, w35, w37, w16 (w38, w39), 40, w47; Cw1, w2, w3, w4, w5.

A previous study had shown that HLA-D polymorphism and, by implication, DR antigens did not add any relevant information (Truog *et al.*, 1975).

A panel of 1428 normal individuals, from the Italian population, typed for HLA was the control for antigen frequencies.

Results

PROBANDS

A total of 39 probands was studied. The sex distribution, 23 males (59%) and 16 females (41%) did not differ significantly. The mean ages of the two groups were comparable (39 years in males *versus* 41 in females), the total age range being 15 to 66 years with a mean of 40 ± 14.66 (Table 1). From the clinical point of view, 9 out of 39 probands showed monolateral SI. The other 30 showed bilateral SI.

Table 1 Age and sex distribution of HLA-B27 positive and negative SI probands

B27	Total (%)	Sex		Age range (years)	(mean $\pm$ S.D.)
		F	M		
+	17 (43.6)	2	15	15-57	37.5 ± 13.49
-	22 (56.4)	14	8	15-66	42.7 ± 15.42
Total	39 (100)	16	23	15-66	40.4 ± 14.66

The distribution of the mono and bilateral involvement did not differ significantly between the two sexes ($P=0.26$).

Seventeen cases (43.6%) were positive for antigen HLA-B27, indicating a highly significant association when compared to a frequency of 4.3% among controls ($\chi^2=108.9$). The relative risk, according to Woolf's formula (1955), was 17.3. No significant deviation was observed for any other HLA specificity.

When the HLA typing was taken into account the following observations emerged: (a) the B27-positive probands were in the majority males (88% 15/23 males, *versus* 2/16 females: $P<0.01$); (b) the onset of the first osteoarticular complaint arose at an earlier age in the B27-positive individuals. This is particularly evident for talalgia ($t_6=3.70$; $P \approx 0.01$); (c) the severity of SI involvement, expressed according to bilateral *versus* monolateral involvement, was significantly greater among B27-positive patients ($P=0.028$) (Table 2).

RELATIVES

Seventy-four first-degree relatives of 26 probands were examined (14 parents, 24 children, 36 sibs; 43 males, 31 females). They were divided into two groups, according to the presence or absence of the B27 antigen in the proband. The prevalence of SI in the two groups is shown in Table 3.

Group 1

Among 20 relatives of 9 B27-positive probands, individuals had clear radiological signs of SI (20%). One of them (a father) was affected by a bilateral SI at an advanced stage and by typical dorsolumbar syndesmophytosis (thus suggesting AS); 1 other (a brother) had definite bilateral SI; the other 2 (a mother and a sister, both in the same family) presented a definite monolateral SI. The HLA typing

Table 2 Radiological SI involvement and HLA-B27 in probands

B27	Total	Monolateral SI	Bilateral
+	17	1	16
-	22	8	14

$P=0.0279$ (Fisher's exact test).

Table 3 Occurrence of SI

First-degree relatives	n	Normal		Affected	
		B27+	B27-	B27+	B27-
<i>9 families of B27- positive probands</i>					
Children	5	2	3	0	0
Sibs	10	4	4	2	0
Parents	5	2	1	2	0
Total	20	8	8	4	0
Affected		B27+ affected			
Total relatives		B27+ relatives			
		= 20%			

showed that all the 4 relatives, for whom a diagnosis of SI was justified, carried the B27 antigen. Thus, the ratio of those affected individuals to the total of the B27-positive relatives (4/12) is 33%.

Group 2

Among 54 relatives of 17 B27-negative probands, only 2 cases were found to be affected by definite monolateral SI. They were two male sibs (belonging to different families) both B27-negative. Thus in this group the frequency of SI is only 3.7%, lower than that found among relatives of B27 positive probands ($P=0.084$ is, however, of marginal significance).

Discussion

Primary radiological involvement of the sacroiliac joints has been recognised to occur at a variable rate in different populations (Gofton *et al.*, 1966; 1972). The epidemiological data available, based mainly on random samples of pelvic x-ray films, always show higher rates of SI in comparison to AS (Table 4). According to the country investigated, the SI prevalence exceeds by 2 to 10 times that of ankylosing spondylitis.

A common aetiopathogenetic mechanism for the two diseases has been suggested by the constant findings of high SI rates among populations with high AS prevalence. The well documented association of both AS and SI with the HLA-B27 antigen (Brewerton and Albert, 1977) is additional evidence of the relationship between the two diseases. On the other hand, the degree of the association with the B27 antigen is clearly different in the two cases: constantly higher for AS, significantly lower for sacroiliitis.

In the majority of HLA studies there is no clear evidence that the authors did discriminate between SI and AS. Among the few exceptions Möller *et al.* (1975) reported a B27 positivity of 70% in a group of 60 SI patients from Scandinavia, while in the same study all AS patients were B27 positive. Our results in 39 SI probands give a B27 frequency of 43.6%. The size of the samples, the genetic background, the environmental conditions, the assessment of diagnosis are all factors that may explain the observed difference.

In any case, the variability in the degree of association between B27 and SI, contrasts with the

Table 4 Prevalence of SI and AS in different populations, compared to the B27 frequency

Population	B27 frequency in controls (%)	AS prevalence (%)	AS B27 positive (%)	SI prevalence (%)	References
Watford (England)	7	0.2	90	1-3	Lawrence (1963); Gofton <i>et al.</i> (1966a); Emery and Lawrence (1967); Brewerton <i>et al.</i> (1973); Brewerton and Albert, (1977)
Turin (Italy)	4.3	0.2	90	1.8	Daneo <i>et al.</i> (1977)
Basel (Switzerland)	10	1.5	93	Not done	Kidd <i>et al.</i> (1977)
Haida Indians (British Columbia)	50	6.7	100	13.6	Gofton <i>et al.</i> (1966b; 1972; 1975)
Pima Indians (Arizona)	18	5.9	64	9-19	Gofton <i>et al.</i> (1972); Calin <i>et al.</i> (1977)
Bella Coola Indians (British Columbia)	25	3.1	100	9.4	Gofton <i>et al.</i> (1972; 1975); ¹
Japan	2-3	0.04	90	Not done	Sonozaki <i>et al.</i> (1975); Shichikawa <i>et al.</i> (1977)
North India (Asia)	3	Not done	95	Not done	Khan (1977); Sengupta <i>et al.</i> (1977)
Ashkenazi Jews	3	Not done	90	Not done	Brautbar <i>et al.</i> (1977)
American blacks	2	Low	50	Not done	Baum and Morris (1971); Good <i>et al.</i> (1976); Khan <i>et al.</i> (1977)
African blacks	< 2	Very low	Not done	Not done	Baum and Morris (1971)
Australian aboriginals	0	0	—	Not done	Cleland <i>et al.</i> (1975)

rather uniform results obtained for AS in all populations tested. This suggests that the so called SI represents a more heterogeneous clinical entity. This interpretation is also in agreement with our observations indicating several differences, at the clinical level, between B27-positive and B27-negative SI patients. The main distinguishing features are the following.

SEX

Whereas the B27-positive probands display an evident male preponderance, the B27-negative ones show no significant difference between sexes (perhaps a slight female excess). Similar findings have been reported by Calin *et al.* (1977).

AGE OF ONSET

First symptoms of the disease together with other related rheumatic complaints seem to appear early in the B27-positive patients. Although in our data these differences are statistically significant only for talalgia, such a trend for the majority of symptoms is worthy of note.

FAMILIALITY

A greater number of SI individuals were found among relatives of B27-positive probands (20% *versus* 3.7% among the relatives of B27-negative probands). Moreover in the former group the secondary cases seem to be more severely affected than in the latter.

In spite of the lack of statistical significance for most of the differences reported, it is none the less justified the attempt of splitting sacroiliitis into two distinct nosological entities. One, recognised through the presence of the B27 marker, shows family data very similar to those reported by our group for AS (Daneo *et al.*, 1977; Kidd *et al.*, 1977). In both diseases the frequency of secondary cases among first-degree relatives is high and confined to carriers of the B27 chromosome. Moreover, the ratio of B27 affected individuals to total B27 relatives, which allows an estimate of the penetrance of the 'illness susceptibility' gene, is very similar: 33% *versus* approximately 35%.

The similarities between B27-positive SI and AS cases allow the suggestion that they represent different levels of expression or different stages of the same genetic pathological entity. Thus in B27 individuals the SI can be regarded as a first step towards the likely (but not certain) development of clearcut AS. It is known, in fact, that involvement of the sacroiliac joints is one of the first signs to appear in AS patients, before spinal symptoms or signs. Often the disease found in relatives of AS

patients has the features of SI, which will only in some cases reach the involvement of the spine. On the other hand, it is interesting that among affected relatives of SI probands in this study at least one shows, besides SI, typical syndesmophytosis as in classical ankylosing spondylitis.

In conclusion, for this variant of SI, which could be regarded as a latent form of AS, the B27 marker plays the same role, as indicator of the 'illness gene' as in ankylosing spondylitis.

The other group of SI patients, recognised by being B27-negative, covers a large proportion (more than 50% in this study) of the total cases affected by sacroiliitis. Apart from the absence of B27, the nosological distinction of this group is outlined by an equal incidence and severity in the two sexes, a less severe involvement of sacroiliac joints, and a low familiarity. In fact the frequency among first-degree relatives (2/54) is close to the reported prevalence in the general population (4/213; $\chi^2 = 0.086$). Within their limitations in size and type, the data reported here do not allow us to accept for B27-negative SI the genetic model of a single major locus with incomplete penetrance, as has been proposed for AS though it is likely valid also for the B27-positive variant of SI. As a matter of fact these data do not even support a significant role of the genotype for the appearance of SI in a B27-negative subject.

The relative role of a major locus *versus* a multifactorial model (with genetic and environmental components) in the aetiology of SI and AS can also be tentatively interpreted from the frequency of B27 antigen among SI and AS patients which often accompany a rather heterogeneous group of so called 'rheumatoid variants' (Crohn's disease, ulcerative colitis, Reiter's syndrome, and psoriatic arthritis).

According to the majority of published data, the frequency of B27 in AS 'complicating' Crohn's disease and ulcerative colitis is significantly higher than in normal controls but significantly lower (60%) than in patients affected by typical uncomplicated AS (Russell, 1977). By contrast SI, which accompanies the above syndromes in about 15% of cases (Wright and Watkinson, 1965), shows a level of the B27 marker of about 20–30%, ie, not significantly lower than the level observed by us for uncomplicated SI. This suggests that the threshold of liability for AS is lowered by the agents responsible for the accompanying disease which can partially substitute and/or dilute the effect of the major B27-associated gene. The same agents also increase the liability for SI (15% *versus* 1.5% in the general population), again suggesting a partially common aetiology between the two diseases.

In conclusion, our observations confirm the usefulness of having a genetic marker associated with a disease not showing a Mendelian pattern of inheritance. In the case of sacroiliitis the relevance of the B27 antigen lies not only in the nosological but mainly in its prognostic implications. In such an heterogeneous disease the HLA-B27 typing may help to distinguish those patients at risk for a probable later evolution towards full expression of typical ankylosing spondylitis.

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