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Viewpoint

B27 positive diseases versus B27 negative diseases

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Of all the known associations between HLA and diseases, the association of B27 with ankylosing spondylitis (AS) is the strongest. The B27 antigen is present in over 90% of patients with AS as compared with the B27 prevalence of 8% in Caucasians in general. A strong but slightly minor association has also been found between B27 and Reiter's syndrome (RS), reactive arthritis (ReA), and acute anterior uveitis (AAU). These diseases are so strongly interrelated, especially in the presence of B27, that one may speak of 'B27 associated diseases'.[1] Many authors regard psoriatic arthritis, also, as a disease associated with B27.[2–4] For reasons which will be discussed below, however, we consider B27 to be associated mainly with the spondylitic part of psoriatic arthritis and not with psoriatic arthritis in general, as others have suggested.[5–8]

The aetiology of these diseases remains elusive. Interaction of environmental and genetic factors has been postulated; nevertheless, a decade after the landmark results on HLA-B27 and its associated diseases[6 9] the nature of the mechanisms underlying these associations is still subject to much speculation.

The association of B27 with its associated diseases is far from complete. This could be explained if, besides B27, other genes near the B locus on chromosome 6, or on other chromosomes, were involved in the pathogenesis.[10–12] From epidemiological and family studies other genetic factors have also emanated to explain the observed incomplete association.[13 14] None of the studies of genetic factors in the pathogenesis of AS, however, clearly indicated genes other than B27.[10 12] Nor did any of the B27 subtypes show a particular association with AS.[15–18]

Strong evidence for B27 as the major genetic susceptibility factor is found in detailed population and family studies, in which no stronger association has been observed other than that between B27 and AS. A stronger B27 association has been found in Caucasians with spondylitis than in their American black counterparts.[19]

In addition to genetic factors, infectious agents have been regarded as a likely cause of primary AS. Several studies by Ebringer *et al* strongly suggested *Klebsiella pneumoniae* in this respect,[20] but other authors could not confirm their results.[21] In reactive arthritis clear cut evidence for causative infectious organisms of urinary and enteric origin have been demonstrated.

In the cases where HLA-B27 is considered to play a part in the pathogenesis of B27 associated diseases, $B27^-$AS, $B27^-$RS, $B27^-$ReA, and $B27^-$AAU are probably the same diseases, but developing along different lines. We have attempted to solve this problem by comparing the clinical pictures of $B27^+$AS, $B27^+$RS, $B27^+$ReA, and $B27^+$AAU with those of their $B27^-$ counterparts.

A review of the literature is given together with the observations made by our own group.

$B27^+$AS versus $B27^-$AS (Table 1)

In the first study on the heterogeneity of AS in black patients Good *et al* observed more serious disease in seven who were HLA-$B27^+$ than in nine who were HLA-$B27^-$.[22] In this study no clinical details were given. Khan *et al* studied clinical differences of $B27^+$ and $B27^-$ black and Caucasian patients with AS.[23 24]

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Table 1 *Differences between B27⁺AS and B27⁻AS*

Clinical details	*Reference*	*B27 positive**		*B27 negative**	
		Number studied	*Prevalence (%)*	*Number studied*	*Prevalence (%)*
Age of onset	29	95	24 (years)	20	38 (years)
Peripheral arthritis	28	88	38	7	14
Peripheral arthritis	29	95	55	20	15
Bamboo spine	28	88	22	7	0
AAU*	24	126	26	11	9
AAU	25	50	28	12	0
AAU	29	95	41	20	15
AAU	30	128	17	17	6
Inflammatory bowel disease	29	95	1	20	9
Psoriasis	8	112	12	10	60
Family history	27	170	+	17	–
Family history	30	128	+	17	–

*AAU=acute anterior uveitis.

They did not find any difference of age at onset, functional class, degree of deformity, *x* ray abnormalities, or the prevalence of peripheral arthritis. The only difference was an increased prevalence of a history of AAU in B27⁺AS patients compared with B27⁻AS patients. This study was confirmed by Nahir and Scharf, who found AAU in B27⁺AS patients only.[25 26] Van der Linden *et al* discovered no clinical differences at all.[27] They found AAU in both B27⁺ and B27⁻ patients. All the patients with AS who had a family history of AS were B27⁺.[27]

Gerber *et al* observed arthritis of the shoulders and lower extremities and the development of a 'bamboo spine' slightly more often in B27⁺AS than in B27⁻AS patients.[28]

On the other hand, the data of Dekker-Saeys,[29] Woodrow and Eastmond,[30] Møller *et al*,[8] and Wagener *et al*[31] did show clinical differences. In B27⁻ disease they found a later onset of AS, milder in its course in respect of the development of a bamboo spine, and thus less aggressive in appearance and subsequently with a better prognosis. They observed more psoriasis and inflammatory bowel disease (IBD) in B27⁻AS and more peripheral arthritis and acute anterior uveitis in B27⁺AS. Family aggregation was seen in B27⁺AS only.[27 30]

Constant findings by nearly all authors were the positive family history of AS and the development of AAU, mostly in B27⁺AS patients.

The discrepancies of the various studies are certainly due to patient selection. In those studies in which no clinical differences were observed between B27⁺AS and B27⁻AS the selection was made from well defined classical AS without associated diseases. In the studies of Dekker-Saeys,[29] Møller *et al*,[8] and Wagener *et al*[31] AS associated with psoriasis and IBD were not excluded. Woodrow and Eastmond did exclude psoriasis and IBD associated with AS.[30] They found five patients with peripheral arthritis resembling psoriatic arthritis. Three of these were B27⁻. One other B27⁻ patient had a sister with ulcerative colitis and AS and a mother with ulcerative colitis.

From these studies one may conclude that B27⁺ AS and B27⁻AS—apart from AAU—are almost identical diseases, but that differences in the clinical picture are caused by the presence of psoriasis or IBD.

In B27⁻AS patients genes other than B27 may provide susceptibility to the development of AS. Possible candidates for such a role are the B7-CREG antigens[32–36] and the antigens associated with psoriasis[37 38] and inflammatory bowel disease.[39]

AS may develop in B27⁻ patients carrying genes associated with psoriasis or inflammatory bowel disease without showing clinical expression of the skin or bowel disease, as was mentioned earlier by Woodrow[38] and Khan *et al*.[33] No firm association between such non-B27 B locus antigens and AS has been found until recently, however.[40–42]

Two different clinical pictures of AS emanate from the above-mentioned studies, as has already been suggested by Dekker-Saeys in 1976.[29] (*a*) *Primary* or *idiopathic* AS, developing early in genetically predisposed persons, triggered by unknown endogenous or exogenous factors, probably infective in origin. These patients are mostly B27⁺. (*b*) *Secondary* AS, triggered by a primary disease, for instance a genital or gut infection, inflammatory bowel disease, or psoriasis. In this group B27 is mostly negative.

Finally, it has to be kept in mind that psoriasis[2 5 43–46] and IBD[5 47 48] itself, even when accompanied by peripheral arthritis, are not associated

with B27. Sacroiliitis without axial involvement in psoriasis is only slightly associated with B27.[2 5 44] In patients with sacroiliitis without axial involvement and IBD no association with B27 has been found.[29 49] When, however, spondylitis accompanies sacroiliitis in psoriasis or IBD the association with B27 is nearly as high as that seen in primary AS.[2 3 46 48] In conclusion, one may state that AS seen in psoriasis or IBD must be considered to be of the primary form.

B27$^+$ReA versus B27$^-$ReA

Yersinia (Table 2)

The first reports of a significant association between B27 and arthritis triggered by an infection with yersinia came from Finland.[50 51] B27 was found in 80% of these patients with reactive arthritis, as was confirmed by others.[52–54]

Heterogeneity between B27$^+$ReA and B27$^-$ReA was studied by Aho *et al.*[51] Table 2 shows that B27$^+$ patients often suffer from inflammation of more than one joint over a longer period of time, frequently complicated by sacroiliitis and AAU. These observations were confirmed by Laitinen *et al*[53] and Leirisalo *et al*,[54] who also found more severe acute disease, including more frequent back pain, urological symptoms, and mucocutaneous manifestations, in B27$^+$ patients than in their B27$^-$ counterparts. RS and AAU were observed in B27$^+$ patients only. The prevalence of erythema nodosum, however, was higher in B27$^-$ patients (Table 2). In the long run B27$^+$ patients had more chronic back pain than B27$^-$ patients. *x* Ray examination in the acute stage of the infection and at follow up showed development of sacroiliitis and spondylitis more often in B27$^+$ patients.

Dequeker *et al*, from Belgium, made a study of 25 patients with yersinia arthritis and found no difference between B27$^+$ and B27$^-$ patients,[55] but their numbers were small. The diagnosis of yersinia arthritis was based on raised agglutination antibody titres (>1/100) and a typical history of oligoarthritis. Tests for the presence of the microbe in the patients or for rising antibody titres or IgA class antibody responses were not performed. They did not

Table 2 *Differences between B27$^+$ and B27$^-$ reactive arthritis after yersinia infection*

Clinical details	*Reference*	*B27 positive*		*B27 negative*	
		Number studied	*Prevalence (%)*	*Number studied*	*Prevalence (%)*
Men	53	49	51	25	24
Duration <1 month	51	43	13	6	67
Duration <1 month	52	31	15	17	41
Duration <1 month	53	49	8	25	40
Duration >2 months	51	43	51	6	0
Duration >3 months	52	31	59	17	12
Duration >3 months	53	49	45	25	24
Monarthritis	51	43	14	6	50
Monarthritis	52	31	6	17	18
Monarthritis	53	49	4	25	10
Polyarthritis	53	49	53	25	28
Bilateral sacroiliitis	51	43	16	6	0
Bilateral sacroiliitis	52	31	10	17	0
Sacroiliitis (acute stage)	54	70	23	16	6
Sacroiliitis (follow up)	54	45	20	13	8
Back pain	54	105	34	39	15
Chronic back pain	54	105	47	39	14
Urological manifestations	52	31	35	17	6
Urological manifestations	53	49	27	25	4
Urethritis	54	105	31	39	3
Reiter's syndrome	53	49	12	25	0
Reiter's syndrome	54	105	37	39	0
AAU	51	43	18	6	0
Iritis	52	31	16	17	0
Iritis or conjunctivitis	53	49	20	25	0
Ocular manifestations	54	105	18	39	0
Carditis	52	31	16	17	0
Erythema nodosum	53	49	2	25	32
Erythema nodosum	54	105	2	39	21
Yersinia titre	53	49	980 (titre)	25	490 (titre)

observe their patients in the acute stage of their arthritis and no mention was made of the time between the start of the infection and the onset of the arthritis. Moreover, one third of the patients did not have a history of diarrhoea at all. Stool cultures were not available, normally being positive within the first two weeks from the onset of the symptoms. The yersinia titre remained raised in a number of cases, even when all symptoms cleared. No mention was made of the nature of these antibodies, though it is known that IgG class antibodies may persist for a long time, even for years, in the circulation of these patients.[56] It is, therefore, difficult to make the diagnosis of ReA after a yersinia infection in all these cases.

Salmonella

Available data from the Scandinavian[50 54 57 58] countries and England[59] on small numbers of patients with reactive arthritis after salmonella infection showed a significantly increased prevalence of B27 of 97%. Heterogeneity between $B27^+$ and $B27^-$ after salmonella ReA was, however, not observed because of the small numbers available. Data obtained by Leirisalo *et al*[54] showed a clinical picture compatible with complete or incomplete RS (only urethritis) in nine $B27^+$ patients. In two of the nine $B27^+$ patients with salmonella reactive arthritis AS developed four years after the infectious arthritis.[54]

Campylobacter jejuni (Table 3)

Reactive arthritis associated with *Campylobacter jejuni* was originally described by Berden *et al.*[60] Kosunen *et al* reported eight cases of ReA among 340 patients with *C jejuni* diarrhoea.[61] Four out of five $B27^+$ patients showed a polyarthritis and a fourfold increase in agglutinating antibodies against *C jejuni*. Three additional patients, of whom two were $B27^-$, showed milder symptoms and a lower

Table 3 *Differences between $B27^+$ and $B27^-$ reactive arthritis after Campylobacter jejuni infection*

Clinical details	*Reference*	*B27 positive*		*B27 negative*	
		Number studied	*Prevalence (%)*	*Number studied*	*Prevalence (%)*
Men	62	18	50	13	62
Mean duration	62	18	110 (days)	13	27 (days)
Polyarthritis	61	5	80	2	0
Polyarthritis	62	18	50	13	8
Extra-articular manifestations	62	18	50	13	38
Agglutination titre increased fourfold	61	5	80	2	50

Table 4 *Differences between $B27^+$ RS and $B27^-$ RS**

Clinical details	*Reference*	*B27 positive*		*B27 negative*	
		Number studied	*Prevalence (%)*	*Number studied*	*Prevalence (%)*
Men	51	36	97	4	50
Fever/weight loss	3	17	83	11	30
Mean sedimentation rate	54	130	66 (mm/h)	30	33 (mm/h)
Sacroiliac involvement	3	17	50	11	18
Sacroiliitis	51	36	18	4	0
Sacroiliitis	65	47	28	16	6
Sacroiliitis (acute phase)	54	115	27	25	12
Sacroiliitis (follow up)	54	81	30	16	6
AS	63	4	25	1	0
AS	65	47	19	16	0
Chronic or relapsing course	3	17	88	11	18
Chronic back pain	54	117	44	23	22
Uveitis	3	17	37	11	0
Iritis (follow up)	54	117	11	23	0
Balanitis, vulvovaginitis	54	130	45	30	10
Mucocutaneous symptoms	54	130	50	30	17
Skin lesions	66	63	40	11	22

*RS=Reiter's syndrome.

C jejuni titre. Van de Putte *et al* recently published a review of 19 studies, including their own.[62] Table 3 shows that compared with their B27$^-$ counterparts the B27$^+$ patients more often have polyarthritis of long duration, complicated by extra-articular manifestations and an increase of the agglutination titre. Data on sacroiliac involvement were too scarce to allow any conclusions.

Shigella

Reactive arthritis after *Shigella flexneri* infection has an 85% prevalence of B27 positivity.[51] Most patients contract Reiter's disease.[51 63] Table 4 gives details of disease heterogeneity.

B27$^+$RS versus B27$^-$RS (Table 4)

McClusky *et al* subdivided 28 patients with Reiter's syndrome into groups based on the course of the disease and extra-articular manifestations. They found a chronic or relapsing course more often in B27$^+$RS patients than in those who were B27$^-$RS.[3] AS expected, extra-articular manifestations were found in B27$^+$RS patients especially. Aho *et al* confirmed these observations.[51] Leirisalo *et al* found significantly increased balanitis, vulvovaginitis, and mucocutaneous symptoms in B27$^+$RS patients compared with B27$^-$RS.[54] Also, more low back pain and abnormal sacroiliac joints were found in

Table 5 *Differences between B27$^+$AAU and B27$^-$AAU**

Clinical details	*Reference*	*B27 positive*		*B27 negative*	
		Number studied	*Prevalence (%)*	*Number studied*	*Prevalence (%)*
Men	67	51	67	39	50
Men	70	22	82	11	36
Men	71	14	67	12	50
Men	72	76	61	93	59
Men	76	50	76	10	60
Men	78	73	71	71	49
Age at onset	78	73	35 (years)	71	43 (years)
Mean age	68	12	33 (years)	21	43 (years)
Duration >3 weeks	67	51	84	39	39
Duration >3 weeks	68	12	75	21	38
Unilateral	76	50	94	10	50
Unilateral	78	73	97	71	79
Cells in anterior chamber	67	51	80	39	44
Cells in anterior chamber	78	73	60	71	18
Fibrin in anterior chamber	67	51	37	39	8
Fibrin in anterior chamber	68	12	100	21	80
Fibrin in anterior chamber	76	50	42	10	0
Fibrin in anterior chamber	78	73	56	71	10
Mutton fat keratic precipitates	76	50	0	10	60
Mutton fat keratic precipitates	78	73	3	71	32
Ptosis	67	51	55	39	23
Posterior synechiae	76	50	76	10	30
Posterior synechiae	78	73	36	71	15
Recurrent attacks	67	51	45	39	13
Recurrent attacks	68	12	92	21	43
Recurrent attacks	71	14	36	12	50
Recurrent attacks	76	50	60	10	30
Mean interval between attack	78	73	100 (weeks)	71	58 (weeks)
Sacroiliitis	69	46	35	33	12
Sacroiliitis	70	22	55	11	27
AS	67	51	22	39	5
AS	71	46	20	33	3
AS	72	76	45	93	8
AS	78	73	39	71	1
RS	67	51	8	39	0
RS	78	73	8	71	0
Low back pain	72	76	60	93	14
Associated rheumatic disease	76	50	42	10	10
Systemic disease	67	51	45	39	13
Systemic disease	68	12	42	21	9
Systemic disease	70	22	55	11	0
Systemic disease	71	14	43	12	8

*AAU=acute anterior uveitis.

$B27^+$RS than in $B27^-$RS. In the follow up period 12% of the $B27^+$RS patients developed AS in contrast with 6% of the $B27^-$RS group. A similar increase in disease severity in $B27^+$RS patients was observed by Schultz *et al.*[64] They analysed the clinical and HLA antigenic profile of 86 Caucasian and 13 black patients with RS. They tried to determine the predictability of certain clinical RS symptoms by any HLA-A or B antigens, or both. The presence of B27 seemed to make the patient with RS more prone to a large total number of clinical features, such as fever, weight loss, low back pain, AS, heel pain, and chronic peripheral arthritis, in addition to acute peripheral joint involvement, especially when the haplotype A1B27 or A2B27 was present. The presence of Bw35 seemed to protect against secondary AS in RS and may be the cause of reduced disease severity of RS in black patients, who have a high prevalence of Bw35.

Thirteen years after an initial RS episode Calin and Fries traced and studied five patients with RS out of a group of 10. Of these five patients with RS, one $B27^-$ patient had minimal disease and was symptom free. The other four $B27^+$ patients had persistent active disease with a chronic course.[63] Nicholls studied 47 $B27^+$ and 16 $B27^-$ men with RS and found more sacroiliitis and AS in the $B27^+$ patients.[65] Willkens *et al* confirmed this persistent disease activity, finding a subsequent chronic course in 63 $B27^+$RS patients compared with 11 $B27^-$RS patients.[66] He observed an increase in skin lesions in $B27^+$ patients as well.

$B27^+$AAU versus $B27^-$AAU (Table 5)

Mapstone and Woodrow described the clinical features in 51 $B27^+$AAU patients as acute inflammation of short duration, frequently occurring unilaterally, and with a preponderance of men. The severity of the attack was measured by protein extravasation into the anterior chamber and the absence of mutton fat keratic precipitates.[67 68] A high prevalence of associated rheumatic disease was observed.[67–74] This B27 associated AAU has been reported to have a favourable prognosis when compared with HLA-$B27^-$AAU.[67 75 76]

The more complicated course of $B27^-$AAU has been attributed to the fact that inflammatory activity in $B27^-$AAU takes more time to resolve. It often becomes chronic, a complication typical of HLA-$B27^-$AAU.[75] Currently, AAU has been classified as an iridocyclitis with a duration of three months at the most.[77] In most studies, however, the term 'acute' has been used to describe the type of inflammation instead of the actual duration of the attack.

Rothova *et al* studied the clinical features of AAU in $B27^+$ and $B27^-$ patients.[78] AAU in this study was defined as an iritis or iridocyclitis that healed completely within a period of three months. Table 5 shows that HLA-B27 associated *acute* AAU is a separate clinical entity. Frequent recurrent and unilateral inflammation of alternating eyes develops, usually in young men, and is severe in the acute stage but with no mutton fat precipitates. The prevalence of ocular complications increased with the number of recurrences. The frequent association with seronegative spondyloarthropathies is confirmed. In the long run, however, visual prognosis did not differ significantly in $B27^+$ or $B27^-$AAU patients.

Discussion

This review shows that the strong interrelationship of AS, RS, ReA, and AAU, especially in the presence of B27, is remarkable. In 1974 Moll and Wright suggested calling this group of strongly interrelated diseases 'the seronegative spondarthritides'.[79–81] It is evident, however, that this name has no reference to AAU, except when AAU is an extra-articular manifestation of AS. Some authors even considered $B27^+$AAU to be a monosymptomatic manifestation or 'forme fruste' of AS.[70 82 83] AAU may be found in all seronegative spondyloarthropathies, with or without sacroiliac joint changes, especially in the presence of B27.[29 56 79 80 84–86]

Radiological sacroiliitis is a necessary condition for the diagnosis of AS,[87 88] which is why Moll and Wright chose radiological sacroiliitis as the pivotal point of the seronegative spondarthritides. Radiological signs of sacroiliitis may exist, however, without other clinical symptoms of AS.[29 82] Ankylosis of the spine is not contracted by all patients,[85 89 90] and spinal syndesmophytes may exist without radiological sacroiliitis in $B27^+$ patients, as has been postulated by some authors.[79 80] Moreover, sacroiliitis may be found in all diseases associated with AS, especially in the presence of B27.[79] Therefore, AAU and sacroiliitis may be considered as two clinical features from a vast number of overlapping symptoms occurring in AS and its related diseases, especially in the presence of B27. It may be better to speak of a syndrome instead of a disease.

The clinical features of this syndrome have been described by Moll and Wright.[79–81] These features are common to all diseases associated with AS. Absence of the rheumatoid factor and subcutaneous nodules has been noted. Peripheral arthritis attacking the joints of the lower extremities and enthesopathy of the Achilles tendon often occur during the course of the disease.

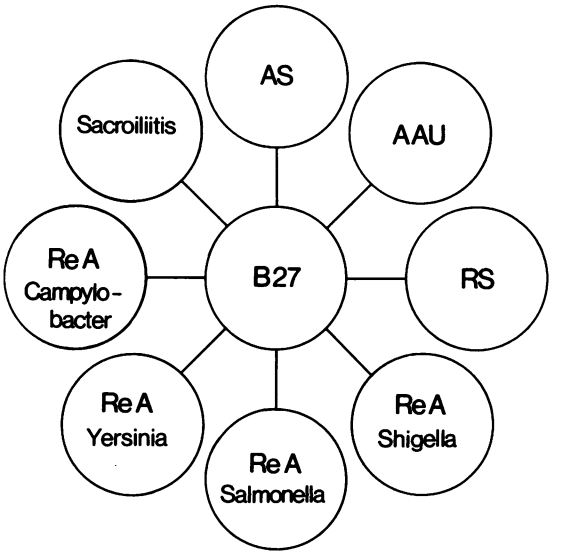

Fig. 1 *B27 associated diseases. AS=ankylosing spondylitis; AAU=acute anterior uveitis; RS=Reiter's syndrome; ReA=reactive arthritis.*

Dekker-Saeys[29] and Møller and Berg[91] suggested the name Bechterew's syndrome for this group of interrelated diseases. HEMRI syndrome (hereditary multifocal relapsing inflammation) has also been suggested as a collective term for the whole group of conditions.[92] These names, however, do not account for the very important role of B27 in these diseases.

We consider B27 to be the pivotal point of these interrelated diseases, as is shown in Fig. 1, and support the name 'the B27 associated diseases'.[1]

The name gives credit to the clinical symptoms and signs of AS and its related diseases. It offers the clinician the possibility of working with a distinct clinical entity. B27⁻AS, psoriatic arthritis, and arthritis in association with inflammatory bowel disease may be regarded as resembling strongly the clinical entities of the B27 associated diseases, but with a distinct pathogenesis. The use of such a specific name may, however, dampen or kill the search for other genetic factors, which undoubtedly exist as was mentioned before.

In this way the various interacting aetiological predisposing genetic and environmental factors in disease susceptibility are accounted for. The part B27 plays in disease susceptibility is not known, though many suggestions have been brought forward. Nevertheless, by placing B27 as a genetic marker in the centre of the associated diseases, further clinical and laboratory research to unravel the pathogenic role of this membrane protein may be stimulated.

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