Epidemiology of B27-associated diseases

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The epidemiology of HLA-B27-associated syndromes is a rapidly expanding field.^{37, 212, 273, 327} The topic can hardly be surveyed in the limited time available. Nevertheless, certain generalisations may be derived from the available, although incomplete, data and inferences drawn for future directions of study.

Ankylosing spondylitis

The prevalence and characterisation of ankylosing spondylitis (AS) depends upon the criteria employed, including, among other factors, sex, family history, race, and B27 status.

Table 1 summarises the prevalence of AS per 1000 Caucasian adults (≥ 15 years) in population studies using routine clinical and radiographic criteria as opposed to AS population survey criteria.^{25, 179} The total prevalence is 1.0 per 1000 population, 1.6 for males and 0.50 for females, or a male to female (M:F) ratio of 3.2:1.

Table 2 shows the percentage prevalence of familial cases of ankylosing spondylitis among siblings of AS probands—that is, 5.0 for males and 3.1 for females—as calculated from studies included in Professor Kellgren's review.¹⁷⁷ The M:F ratio among familial cases is 1.6:1, and the overall frequency is 4%.

A heritability factor (K) may be derived by forming a ratio of the prevalence of ankylosing spondylitis in relatives over the prevalence in the general population.¹⁷⁷ The K value is 31 for males versus 62

Table 2 Percent of familial cases of ankylosing spondylitis (AS) among siblings of AS probands*

First author	Males		Females		Both sexes	
	No. sibs	%	No. sibs	%	No. sibs	%
Stecher, R. M. ^{295a}	86	3.5	72	4.2	158	3.8
de Blécourt, J. J. ²⁹	200	7.5	201	4.5	401	6.0
O'Connell, D. ^{239a}	184	4.3	110	0.9	294	3.1
Karten, I. ^{173a}	68	1.5	101	2.0	169	1.8
Total series	538	5.0	484	3.1	1022	4.0

*Studies cited by Kellgren.¹⁷⁷

for females ($P < 0.05$). It is 40 for both sexes combined, as originally derived by Kellgren.¹⁷⁷

From multiple studies Woodrow³²⁷ calculated a combined relative risk of AS in B27-positive versus B27-negative people of 76, and the relative risk is presumed to be equal in males and females. The overall K value is almost exactly half the combined relative risk, which is consistent with the Mendelian autosomal codominant inheritance of B27, its almost complete association with ankylosing spondylitis, and assuming equivalent ascertainment of ankylosing spondylitis in the studies.

Pronounced racial differences in the prevalence of AS, shown in Table 3, seem to be mainly but not completely correlated with the varied prevalence of B27 in the population,³²⁷ which ranges from 50% in Haida Indians of British Columbia to about 1% in native black Africans.^{52, 131} Reported AS prevalences,

Table 1 Prevalence (P) of ankylosing spondylitis (AS) per 1000 adult (≥ 15 years) Caucasians in population studies using routine clinical and radiographic criteria

First author	Males		Females		Both sexes	
	No. surveyed	P	No. surveyed	P	No. surveyed	P
Holst, H. ¹⁵⁸						
Town	9636	3.1	11 439	0.6	21 075	1.8
Rural	44 908	0.7	43 333	0.3	88 241	0.5
de Blécourt, J. J. ²⁹	1205	1.7	1236	0.0	2441	0.8
Lawrence, J. S. ¹⁹⁸	1060	4.0	1173	0.0	2233	1.8
Mikkelsen, W. M. ²²⁴	2239	5.8	2449	0.8	4688	3.2*
Gomör, B. ¹³²	3080	4.0	3390	0.8	6470	2.3
Carter, E. T. ^{56a}	23 800	2.0	28 800	0.7	52 600	1.3
Total series	85 928	1.6	91 820	0.50	177 748	1.0

*'Probable' AS (clinical criteria only).

Table 3 *Prevalence (P) of definite ankylosing spondylitis per 1000 adult males in population studies using New York survey criteria compared with general population prevalence of HLA-B27*

First author	Population surveyed*	No.	P	B27
Gofton, J. P. ¹³¹	Haida (20+)	158	60	50
	Bella Coola (15+)	141	21	25
	Pimas (15+)	209	45	18
Solomon, L. ²⁹²	S. African blacks (16+)	508	2	1

*Age groups in parentheses.

defined according to the New York criteria,²⁵ have ranged from 60 per 1000 Haida males¹³⁰ to a rare occurrence in South African blacks.²⁹²

The prevalence of ankylosing spondylitis in Pima males seems higher than expected.⁵² Unusual relationships have been reported between radiological sacroiliitis, sex, familial status, and the incidence of HLA-B27 in the Pimas.⁵² Grade 2+ sacroiliitis was more prevalent in females (24%) than in males (16%) but no association was found with B27 in females. The incidence of sacroiliitis in first degree relatives of probands with sacroiliitis was the same as in the general population controls. Also the association of sacroiliitis in males with B27 (relative risk 4.5) was less than in other Indian tribes²⁹² or other races.³²⁷

The sex ratio in AS seems to vary significantly, depending on the severity of disease. Male preponderance is usually reported in clinically advanced AS whereas the sex ratio approaches equality with milder axial involvement, with or without peripheral arthritis.⁸²

AS rarely starts in the first decade or after the age of 50. The incidence of cases rises sharply from about the age 15 to the age of 30.^{32, 173} The association of B27 with AS decreases significantly as the age of onset rises³¹⁷, suggesting that secondary, non-B27-related factors may be contributing to the onset of the disease in older people.

Available studies of AS suggest that genetic factors associated with B27 are the most important determinants of susceptibility, but that they alone are neither sufficient nor exclusive. Age and sex seem to modify the disease, as may ethnic factors. Secondary forms of AS or sacroiliitis may predominate in certain ethnic, sex, and age groups.

Reiter's syndrome and other postinfection reactive arthritis syndromes

Reiter's syndrome (RS) and other types of post-infection reactive arthritis syndromes are also related to B27. Their overlapping features and varied occurrence in the same individual or in families point to a common underlying host predisposition.

Table 4 summarizes the incidence of RS, salmonella, and yersinia reactive arthritis after enteric or venereal infections. These studies in Caucasians indicate that about 1%–3% of people with such infections have a delayed acute sterile arthritis reaction. Paronen's study²⁴⁴ was done under adverse, war-time conditions and under-ascertainment might be expected. The *S. enteritidis* finding is from a small number of cases and requires confirmation. The incidence of yersinia reactive arthritis is biased by a selection of patients with high agglutinin titres,⁵ which suggests that

Table 4 *Incidence of RS, salmonella, and yersinia reactive arthritis after enteric or venereal infections*

	No. infected	No. (%) with arthritis	Comments
Reiter's syndrome			
Postdysenteric			
Finland (1944) ²⁴⁴	150 000	344 (0.2)	<i>Shigella flexneri</i> epidemic, 39 (78%) of 50 patients tested had B27
US naval vessel (1962) ²³⁸	602	9 (1.5)	<i>Shigella</i> epidemic, 4 of 5 patients tested had B27
Postvenereal			
London (1942–56) ⁶⁸	22 010	182 (0.8)	All urethritis cases
Manchester (1951–7) ¹⁹¹	8560	59 (0.7)	
All urethritis cases	3500	59 (1.7)	
Non-gonococcal arthritis			
Salmonella reactive arthritis			
Heinola (1961–62) ³¹⁶	329	8 (2.4)	<i>S. typhimurium</i> -specific
	426	8 (1.9)	All salmonella strains
Winchester, UK (1963–69) ³²²	295	6 (3.0)	All salmonella strains
		3 (2.5)	<i>S. typhimurium</i>
		3 (9.5)	<i>S. enteritidis</i>
Copenhagen (1964–74) ¹²¹	366	6 (1.6)	All salmonella strains, 3 of 5 patients tested had B27
Yersinia reactive arthritis			
Finland (1968–70) ⁵	334	104 (31.1)	Titres of 1:160+ selected from an original 6030 patients investigated for yersinia infection
<i>Y. enterocolitica</i>	304	101 (33.3)	
<i>Y. pseudotuberculosis</i>	30	3 (10.0)	

severity of infection or intensity of host response in susceptibles may influence the development of reactive arthritis.

Follow-up of some of these patients with post-dysenteric RS^{55, 268} and salmonella reactive arthritis¹²¹ showed a prevalence of B27 in the range of 60%–80%. This has also been found in other patients with these syndromes as well as in patients with yersinia arthritis.^{2, 193}

As with idiopathic ankylosing spondylitis, age, sex, and possibly ethnic factors, influence the expression of these diseases. Cases of postvenereal RS are rare in women, comprising about 2% of the total cases,⁶⁸ but cases of postenteric RS in women are relatively more common, comprising at least 10% of cases.²⁴⁴ Sex predisposition to yersinia arthritis is equal in B27-positive individuals but the F:M ratio is 3:1 among B27-negative individuals.¹⁹³ RS rarely begins in the first decade¹⁶⁵ or after the age of 50,⁶⁸ not unlike the other B27 reactive arthritis syndromes. Postenteric RS is rare in the US and the UK, unlike continental Europe, Asia, and Northern Africa.¹⁶⁵

Available data support the thesis that genetic and host factors influence susceptibility to various stimuli, including recognised infectious agents, which result in a spectrum of articular and systemic manifestations.

Psoriatic arthropathy

Studies of the prevalence of B27 in patients with psoriatic arthropathy are summarised in Table 5, comparing peripheral arthritis alone with radiographic sacroiliitis or with AS when specified.^{40, 217} Except for isolated reports, B27 was only weakly or not at all associated with peripheral arthritis alone,

whereas it was consistently associated with radiographic sacroiliitis and AS, the average frequencies being 15%, 49%, and 71% respectively. The prevalence is not homogenous within each category. These data suggest the possibility of differences in definition and severity of disease among the series both in arthritis and psoriasis.

Males predominated among cases of B27-positive spondylitis²²³ and in the AS group compared with cases of radiographic sacroiliitis and peripheral arthritis.^{95, 195} Radiographic spondylitis without sacroiliitis tended to show a low correlation with B27—only 4 (20%) out of 20 patients culled from several series.^{82, 95, 195} These findings suggest different types of spinal lesion in psoriasis.

Neither sex nor age seemed to influence predisposition to the peripheral arthritis syndrome, which, in view of family studies²²⁹ and recent evidence of an association with BW38,¹⁰² may have a separate genetic predisposition.

Inflammatory bowel disease arthropathy

Table 6 summarises studies of the prevalence of B27 among patients with inflammatory bowel disease with peripheral arthritis alone, radiographic sacroiliitis without spondylitis, and AS. Overall results indicate a frequency of 7% among patients with peripheral arthritis alone, 17% among those with radiographic sacroiliitis, and 54% among those with AS.

Because of clinical differences, the peripheral arthropathy of inflammatory bowel disease has been considered a secondary extraintestinal complication of active bowel disease and different from AS, which also is an associated manifestation.^{150, 220} The B27

Table 5 Prevalence of HLA-B27 among patients with psoriatic arthropathy. Comparison of peripheral arthritis alone, radiographic sacroiliitis or spondylitis, and ankylosing spondylitis (AS) when specified

First author	Peripheral arthritis		Sacroiliitis*		AS specified	
	No.	No. (%) B27	No.	No. (%) B27	No.	No. (%) B27
McCluskey, O. E. ²¹⁷	8	—	6	6 (100)		
Brewerton, D. A. ⁴⁰	41	10 (24)	9	4 (44)*	10	9 (90)
Zachariae, H. ³⁴⁰	29	6 (21)	15	7 (47)		
Karvonen, J. ¹⁷⁴	40	11 (28)	25	15 (60)		
Metzger, A. L. ²²³	17	3 (18)	23	8 (35)		
Marcusson, J. ²⁰⁸	3	2 (67)	22	10 (46)		
Amor, B. ¹²	18	—	12	5 (42)		
Lambert, J. R. ¹⁹⁵	54	5 (9)	9	7 (78)*	7	5 (71)
Eastmond, C. J. ⁹⁵	33	7 (21)	15	11 (73)*	7	7 (100)
Roux, H. ²⁶²	68	5 (7)	22	2 (9)*	18	9 (50)
Espinoza, L. R. ¹⁰²	22	1 (5)	6	5 (83)		
Total series	333	50 (15)	164	80 (49)	42	30 (71)

*Excluding ankylosing spondylitis patients when specified separately.

Chi-square homogeneity tests: Peripheral arthritis 26.8, 10 df, $P < 0.01$. Sacroiliitis 12.3, 6 df, $P < 0.05$. Ankylosing spondylitis 8.5, 3 df, $P < 0.05$.

Table 6 *Prevalence of HLA-B27 among patients with inflammatory bowel disease. Comparison of peripheral arthritis alone, radiographic sacroiliitis without spondylitis, and ankylosing spondylitis*

First author	Peripheral arthritis alone		Radiographic sacroiliitis		Ankylosing spondylitis	
	No.	No. (%) B27	No.	No. (%) B27	No.	No. (%) B27
Brewerton, D. A. ⁴⁰	8	1 (13)	2	—	18	13 (72)
Morris, R. I. ²³¹	8	—			8	6 (75)
Russell, A. S. ²⁶⁶	66	3 (5)			11	10 (91)
Jacoby, R. K. ¹⁶⁷	71	5 (7)	3	—	3	1 (33)
Mallas, E. G. ²⁰³	29	—	17	7 (40)	7	5 (72)
Deshayes, P. ⁸³			1	—	6	4 (67)
Hyla, J. F. ¹⁶¹			11	1 (9)	4	3 (75)
Huau, J. P. ¹⁶⁰			7	—	15	5 (33)
Dekker-Saey, B. J. ⁷⁹	14	4 (29)	11	1 (9)	4	2 (50)
Total series	196	13 (7)	52	9 (17)	76	39 (54)

Chi-square homogeneity tests: Peripheral arthritis alone 14.4, 5 df, $P < 0.05$. Radiographic sacroiliitis 10.5, 6 df, NS. Ankylosing spondylitis 12.6, 8 df, NS.

results would support this belief. Radiographic sacroiliitis, which is significantly increased in inflammatory bowel disease,^{78, 80, 161} seems to have a low, if any, association with B27, which again suggests a secondary process different from idiopathic AS. The incidence of B27 among patients with AS and inflammatory bowel disease is significantly greater than normal but considerably less than that seen in idiopathic AS, estimated to average 88% in Caucasians.³²⁷

The possibility of a sizable proportion of cases of 'secondary' AS in inflammatory bowel disease was raised recently. Nine patients with AS and Crohn's disease were seen who were all negative for B27 and whose AS had started at least two years after the onset of severe, protracted inflammatory bowel disease.⁸⁰ The existence of such cases of secondary AS would help to explain both the higher incidence of AS in inflammatory bowel disease and the lower proportion of B27 with such concurrence than with idiopathic AS.

Avenues for future research

Synthesis of the available, incomplete findings is difficult, subjective, and liable to misinterpretation. Nevertheless, until more complete data are accumulated working hypotheses can be useful if they can be tested. Table 7 outlines potential newer areas for future research, emphasising spondylitis and radiographic sacroiliitis as a model.

Evidence is accumulating for secondary forms of these disorders, presumably operating independently or distantly from B27-related factors. Careful study of these syndromes, comparing them with B27-positive idiopathic AS may reveal common as well as distinct pathophysiological mechanisms. A possible direct role of B27 and related surface antigens in disease pathogenesis has been proposed.^{17, 308}

Table 7 *Promising avenues for future research in ankylosing spondylitis and sacroiliitis*

<i>A. Secondary forms of spondylitis or sacroiliitis</i>
(1) Lower incidence of B27 in older onset AS ³¹⁷
(2) 'Osteophytosis' in older onset AS ²⁵⁷
(3) Sacroiliac fusion with aging ³²
(4) Sacroiliac fusion in paraplegics with spinal cord injuries ³²
(5) RSI in Pima women not related to B27 ⁵²
(6) Spondylitis without sacroiliitis in psoriasis ^{95, 195}
(7) AS and RSI in IBD not related to B27 ^{79, 161}
<i>B. Possible direct role for B27 and related antigens</i>
(1) Cross-reactive antigens (B7, BW22, BW42) in B27-negative patients ¹⁷
(2) HLA-related hormone control ¹⁶⁴ and endocrine disease associations ^{307, 313}
(3) Suggested HLA receptor function for hormone interaction ³⁰⁸
(4) Strikingly high association of B27 with idiopathic AS ^{37, 327}
(5) Lack of evidence of HLA D or DR associations in AS ^{36, 180}

Abbreviations: AS = ankylosing spondylitis; RSI = radiographic sacroiliitis; IBD = inflammatory bowel disease.

Although infectious agents or other antigen receptor functions have been mainly suspected,¹⁷ hormone and endocrine interactions might be as likely.^{164, 307, 308, 313} The latter possibility would seem even more consistent with the prominent age of onset and sex patterns in idiopathic AS. A more direct sex hormone interaction of B27 may be related in a mysterious fashion to reproductive functions that might favour persistence in the population of the gene(s) controlling B27 and related antigens. Also axial muscle tension may be a factor in these degenerative spinal syndromes.

General discussion

DR. A. CALIN: The Pima women appear to have 'primary ankylosing spondylitis' in that they are young, often B27-negative patients with uveitis and without any of the other B27-associated conditions, which occur very rarely in the Pima.