Non-secretion of ABO blood group antigens as a host susceptibility factor in the spondyloarthropathies

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Abstract

Gram negative bacteria precipitate reactive arthritis and may be concerned in the pathogenesis of ankylosing spondylitis and other spondyloarthropathies. Susceptibility to many infectious agents is associated with ABO blood group or secretor state, or both. The distribution of the ABO blood group or secretor state, or both, was therefore determined in 87 patients with ankylosing spondylitis and 32 with other forms of spondyloarthropathy.

The prevalence of non-secretors was significantly increased in the total patient group (54/114; 47%) and in the subgroup with ankylosing spondylitis (41/84; 49%) compared with local controls (89/334; 27%) ($p < 0.001$). Other subgroups of patients showed a similarly increased prevalence of non-secretion (33-47%). The distribution of ABO blood groups did not differ between patients and controls.

The association between non-secretor state and ankylosing spondylitis strengthens the hypothesis that ankylosing spondylitis is a form of reactive arthritis. It also suggests several pathogenic mechanisms which may be relevant to the initial host-parasite interaction in ankylosing spondylitis.

Introduction

An infectious aetiology for ankylosing spondylitis has been postulated on several occasions, and many workers consider this disease to be a form of reactive arthritis.^{1,2} The hypothesis that the aetiology of ankylosing spondylitis is related to the gut is based on the abnormalities of the bowel that occur in other spondyloarthropathies³ and on analogy with the reactive arthritis that may occur after gastrointestinal infection.⁴ These associations suggest that Gram negative bacteria acting at the gut mucosal surface may be important in the pathogenesis of ankylosing spondylitis. Investigators have examined the role of faecal klebsiella^{5,7} and the interaction of these and similar organisms with HLA-B27,^{8,9} but no clear relation among enterobacteria, HLA-B27, and ankylosing spondylitis has emerged. It may therefore be pertinent to consider aspects of the host-parasite relation other than HLA-B27, and in particular those host factors associated with infection by Gram negative bacteria.

Blood group specificities of the ABO system are genetically determined, stable host characteristics which have been associated with susceptibility to some infectious diseases. The prevalence

of blood group O is increased in patients with typhoid,¹⁰ paratyphoid,¹⁰ and cholera¹¹; group B is increased in patients with gonorrhoea,¹² chlamydial infections (unpublished observations), urinary tract infection caused by *Escherichia coli*,¹³ and in children with Gram negative enteric infections¹⁴; and there are reports of an increased prevalence of group A among patients with meningococcal meningitis.¹⁰ By contrast, a normal distribution of blood groups is found among patients with diphtheria, brucellar infections, and whooping cough.¹⁰ At least two infections associated with an increased prevalence of the B blood group, gonorrhoea and chlamydia, may precipitate reactive arthritis.⁴

A second genetically controlled host characteristic which has been associated with susceptibility to infection is the inability to secrete the water soluble glycoprotein forms of the ABO blood group antigens. The prevalence of non-secretors is increased among patients with cholera,¹⁵ urinary tract infection caused by *E. coli*,¹³ candidiasis,¹⁶ meningococcal meningitis,¹⁷ and pneumococcal infections,¹⁷ but not among those with tuberculosis,¹⁰ leprosy,¹⁰ or gonorrhoea.¹² Though only a few studies have been reported, a pattern is emerging of an association between non-secretion of blood group antigens and susceptibility to infections of the mucosal surfaces.

These observations led us to examine the hypothesis that there would be an increased prevalence of blood group B or non-secretor state, or both, among patients with ankylosing spondylitis and other spondyloarthropathies. As concentrations of IgA (the immunoglobulin associated with protection of mucosal surfaces) are raised in ankylosing spondylitis,^{18,19} and reportedly influenced by secretor state,^{20,21} we have also determined IgA concentrations in the serum and saliva of our patients.

Patients and methods

We studied 119 patients with clinically well defined spondylarthritides selected at random from the population attending outpatient clinics at the rheumatic diseases unit of the Northern General Hospital over two years. Patients were classified into four categories according to their medical history: ankylosing spondylitis (87 patients), reactive arthritis (22), and radiological sacroiliitis (with or without ankylosing spondylitis) (a) associated with inflammatory bowel disease (three patients) or (b) associated with psoriasis (seven patients). Patients with ankylosing spondylitis fulfilled the New York criteria,²² and those with reactive arthritis fulfilled criteria for definite Reiter's disease²³ (14 patients) or postinfective reactive arthritis²⁴ (eight patients).

When possible patients' records were analysed for HLA state (55 patients) and for a history of ocular inflammation (101) or inflammatory arthritis of peripheral joints (100). A single sample of venous blood and saliva was collected from each of 113 patients. A further five patients provided blood, but no saliva, and one provided saliva only.

ABO Blood group was determined in 118 patients by agglutination of red cells with appropriate antisera. Secretor state was determined in 114 patients by the haemagglutination inhibition assay using saliva, as described.²⁵ Controls were 334 randomly selected normal people attending the Edinburgh blood donor centre during 1981.¹³ IgA Concentrations in samples of serum (98 patients) and saliva (97) which had been stored at -20°C were determined by single radial immunodiffusion with commercially prepared plates (Behring Diagnostic, Hounslow).

Statistical analyses were by χ^2 test, using Yates's correction for continuity in fourfold tables. Relative risk (odds ratio) was calculated by simple proportion. Ninety five per cent confidence limits for relative risk were calculated using natural logarithm conversion.

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Results

Tables I and II show the distribution of ABO blood group and secretor state in the patients and controls. There was a significant increase ($p < 0.001$) in the proportion of non-secretors in the total patient group (54/114; 47%) compared with the local control population (89/334; 27%). The relative risk for spondyloarthropathy in non-secretors was 2.5 (95% confidence interval 1.6-3.8). The increase in non-secretors was evident in all subgroups of patients and achieved statistical significance ($p < 0.001$) in both the total group with sacroiliitis (46/97; 47%)—that is, all patients with radiological sacroiliitis irrespective of disease category—and the group with ankylosing spondylitis (41/84; 49%). Nine out of 20 patients with reactive arthritis

Discussion

Secretion of blood group antigens into body fluids is a dominant, genetically determined characteristic. Roughly 25% of people throughout the world are recessive for the secretor (*Se*) gene, genotype *se,se*, though the proportion varies in some populations.²⁶ Our control group shows that the local population had a proportion of non-secretors similar to but slightly higher than the expected frequency, as is usual among populations of Celtic origin.

This study found a significantly increased prevalence of non-secretors of blood group antigens among patients with spondylo-

TABLE I—Distribution of ABO blood group among patients with spondyloarthropathies

	No tested	No (%) with blood group				χ^2 v control	p
		O	A	B	AB		
Control population	334	173 (52)	104 (31)	42 (13)	15 (4)		
Total patient group	118	49 (42)	47 (40)	17 (14)	5 (4)	3.93	>0.10
Total group with sacroiliitis*	99	41 (41)	39 (39)	14 (14)	5 (5)	3.44	>0.10
Ankylosing spondylitis	86	35 (41)	34 (40)	13 (15)	4 (5)	3.51	>0.10
Reactive arthritis	22	10 (45)	8 (36)	4 (18)	0	N/A	
Sacroiliitis associated with inflammatory bowel disease	3	1 (33)	2 (67)	0	0	N/A	
Sacroiliitis associated with psoriasis	7	3 (43)	3 (43)	0	1 (14)	N/A	

N/A=Not applicable.

*All patients with radiological sacroiliitis irrespective of disease category.

TABLE II—Secretor state of patients with spondyloarthropathies

	No tested	No (%) of non-secretors	χ^2 v control	p	Relative risk (95% confidence interval)
Control population	334	89 (27)			
Total patient group	114	54 (47)	15.85	<0.001	2.5 (1.6-3.8)
Total group with sacroiliitis*	97	46 (47)	14.13	<0.001	2.5 (1.5-4.2)
Ankylosing spondylitis	84	41 (49)	14.37	<0.001	2.6 (1.5-4.6)
Reactive arthritis	20	9 (45)	2.32	>0.10	2.3 (0.7-7.0)
Sacroiliitis associated with inflammatory bowel disease	3	1 (33)	N/A		
Sacroiliitis associated with psoriasis	7	3 (43)	N/A		

N/A=Not applicable.

*All patients with radiological sacroiliitis irrespective of disease category.

(45%) and three out of seven with sacroiliitis associated with psoriasis (43%) were non-secretors, proportions similar to that in the group with ankylosing spondylitis.

There was no evidence that the distribution of ABO blood group among the patients was different from that among local controls ($p > 0.10$), and in particular no evidence of an increased prevalence of blood group B. The blood group distribution was similar in each disease category.

Analysis of IgA concentrations and clinical features in the total patient group showed few differences between secretors and non-secretors. There was no evidence of differences in serum or salivary IgA concentrations between the two groups (table III); eye lesions were more common among

TABLE III—Secretor state and geometric mean IgA concentrations (SD in parentheses) in patients with spondyloarthropathies. Values are IU/ml

	Serum IgA	Salivary IgA
Secretors (n=51 serum, 50 salivary)	176.8 (1.5)	4.3 (1.8)
Non-secretors (n=47 serum, 47 salivary)	172.6 (1.9)	4.3 (1.7)

non-secretors (17/48; 35%) than secretors (11/53; 21%), but not significantly so; peripheral joint disease was less common among non-secretors (24/47; 51%) than secretors (35/53; 66%), but again the difference was not significant.

Data on HLA typing were available for 55 patients; 50 were B27 positive and five B27 negative. Three of the B27 negative patients were non-secretors and two were secretors.

arthropathies. There are several possible explanations. The gene for secretion may be linked to another which affects susceptibility to disease or immune responsiveness; the product of the *Se* gene may modify antigens on cells of host or parasite; or blood group antigens may themselves be important in determining susceptibility to these diseases.

Family studies of ankylosing spondylitis and reactive arthritis show that genetic determinants additional to HLA-B27 are necessary for the development of these diseases.^{27,28} It has been suggested that such additional genes are concerned with the functioning of the immune system, and it is therefore tempting to speculate that there is a genetic link between secretor state and immune responsiveness. There is evidence that the *Se* gene forms part of a linkage group on chromosome 19 with complement component C3, but this is the only known immunological function coded for nearby: genes coding for HLA and most other immune determinants are on chromosome 6.²⁹ A single report that salivary IgA concentrations are reduced in non-secretor adults²¹ suggests that IgA deficiency may be responsible for increased susceptibility to infection in non-secretors, which in turn might predispose to reactive arthritis and spondylarthritides. Our data do not support such a hypothesis. Our studies suggest that non-secretion increases the relative risk for ankylosing spondylitis and reactive arthritis, albeit only twofold to threefold. Hence the gene determining secretor state is possibly in itself a subsidiary determinant for these diseases. Family studies will be required to assess the combined relative risk of being HLA-B27 positive and the non-secretor genotype *se,se*.

The biological role of the *Se* gene is not clear, but there is

biochemical evidence that *Se* is a structural gene encoding a specific fucosyltransferase. At least two such enzymes are concerned with the synthesis of blood group specificities, adding fucose residues to one of several types of precursor chain. Evidence suggests that the *Se* gene product preferentially uses the type I chain as substrate.³⁰ Possibly this enzyme glycosylates other structures such as HLA or other cell surface antigens, or even antigens on invading micro-organisms. Any such modification of antigens on host tissue or infecting agent might affect the balance of the initial host-parasite interaction.

The main differences between secretors and non-secretors are related to the antigens present in their body fluids. With the exception of the extremely rare Bombay phenotype, all secretors have the water soluble form of the H antigen (the antigen of blood group O), and the 94% who possess the Lewis blood group gene have *Le^b* antigen. People of the appropriate blood groups will also secrete water soluble forms of the A and B antigens. Non-secretors do not have A, B, H, or *Le^b* antigens in their body fluids, but the 94% with the Lewis gene have a different form of the Lewis antigen, *Le^a*. ABH antigens occur in two forms, a glycolipid which forms part of the structure of a cell and a glycoprotein which is found in body fluids. Lewis antigens occur as glycolipids in the plasma and as glycoproteins in secretions; they do not form part of the structure of cells but are passively adsorbed to cell surfaces.

Much epidemiological evidence suggests that ankylosing spondylitis and reactive arthritis occur in genetically predisposed subjects after exposure to micro-organisms. Finding an association between secretor state and spondyloarthropathies suggests a possible role for blood group antigens in these diseases. Non-secretion appears to be a marker associated with infections of the mucosal surfaces^{13 15 16} and may be important in the colonisation stages of an infectious process. We suggest two models to explain the increased susceptibility of non-secretors to initial infection: *Le^a* in the body fluids of non-secretors may act as a receptor for infecting micro-organisms; or H or *Le^b*, or both, in the body fluids of secretors may inhibit the attachment of organisms. These two mechanisms are not mutually exclusive. It is unlikely that water soluble forms of the A and B antigens play a part in the spondyloarthropathies, as our studies showed no association between these blood groups and ankylosing spondylitis or reactive arthritis.

There is at present little direct evidence that the ABO or Lewis blood groups act as receptors for micro-organisms. Nevertheless, antigens of other blood group systems do act in this way,^{31 32} and recent work from our laboratory has identified the *Le^a* antigen as a receptor for certain strains of *Candida*.³³ Indirect evidence for a receptor role for these antigens comes from finding that *E coli* binds in greater numbers to non-secretor than secretor cells,³⁴ and from studies showing that attachment of micro-organisms may be inhibited by glycoconjugates in body secretions.^{35 36} Experiments are under way in our laboratory to see whether any of these mechanisms are operative in the interaction of arthritogenic Gram negative bacteria with secretor and non-secretor cells of patients with ankylosing spondylitis and controls.

Finding that non-secretion is associated with ankylosing spondylitis and reactive arthritis, together with the accumulating evidence of an association between non-secretion and mucosal surface infections, strengthens the hypothesis that ankylosing spondylitis is a form of reactive arthritis.

Though the increased relative risk for spondylarthritis associated with non-secretion is less than that associated with HLA-B27, non-secretion is nevertheless a host susceptibility factor for these diseases. Moreover, it may be particularly important in pointing the way to our understanding of the pathogenetic mechanisms in the initiation of disease in susceptible people.

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