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HLA frequencies in less common arthropathies

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Robitaille, A., Cockburn, C., James, D. C. O., and Ansell, B. M. (1976). *Annals of the Rheumatic Diseases*, **35**, 271–273. **HLA frequencies in less common arthropathies.** There was no increased incidence of HLA-B27 in patients suffering from rubella arthropathy, when compared to both the Westminster controls and a group of patients with arthritis secondary to dysentery who nearly all possessed this allele.

Arthritis has been described with a number of viral infections (Denman, 1975; Panush, 1974), notably rubella (Heggie and Robins, 1969; Yanez and others, 1966; Lerman and others, 1971), mumps (Caranasos and Felker, 1967), chickenpox (Friedman and Naveh, 1971), infectious hepatitis, infectious mononucleosis, and serum hepatitis (Smith and Sanford, 1967). However, the incidence of arthritis is low and why one person develops it while the majority do not, remains uncertain. Because of this it was decided to look at a group of patients in whom arthritis was thought to be associated with a preceding viral infection and compare the incidence of HLA-B27 with a group of patients with 'reactive arthritis' following a bacterial infection.

Aho (1974) used the term 'reactive arthritis' for an acute arthritis occurring in association with an infection elsewhere in the body but without the bacteria being present in the joint. He then reported that 88% of patients (43/49) with arthritis secondary to Yersinia infection possessed the histocompatibility antigen B27 while the 22 patients infected with Yersinia but not exhibiting articular manifestations had no increase of B27 when compared with the controls (14% in Finnish controls) (Aho and others, 1974). Similarly, he noted a significant increase of the same allele in those who had an arthropathy associated with Salmonella or Shigella infections (Aho and others, 1975).

Material

Our cases were divided in three groups, depending on the aetiology of their arthritis. Most of the patients included had been diagnosed in the past (1955–1974); these were recalled for reappraisal. In addition, a few cases happened to attend during the study. A full clinical examination was performed and blood tests and radiographs were done according to their need. This allowed us to look carefully at the original diagnosis.

In the first group a diagnosis of presumed rubella arthropathy was made on the presence of an arthropathy, which developed in the course of a clinical attack of rubella, and was supported whenever possible by a rising titre to rubella, or when unavailable by a history of contact with another known case of rubella. The term 'presumed' is used because many of these patients were referred too late to allow the typical rise in antibody titres to be detected. There were 23 such cases, of which 16 were female.

The second group consisted of 17 cases (12 females, 5 males) of transient arthritis associated with a number of different viral infections. They are grouped together either because of their limited number or because of lack of specificity. The diagnosis of 'viral arthritis' relied on different criteria: an arthropathy developed during a clinical attack of mumps (2 cases), or of glandular fever (3 cases); there was a rise in the serum of antibody titre to parainfluenza 1 (1 case), to cytomegalic virus (1 case), to respiratory syncytial cells (1 case); in 9 cases a transient arthropathy had occurred with a history suggestive of viral infection, and accompanied by leucopenia with no evidence of other diseases, either then or now.

The last group of 13 patients represented cases of arthritis accompanying or immediately following a dysentery infection. 3 cases (1, 4, 6) had an increasing titre and 3 other cases (2, 3, 5) had an increased titre to a Salmonella. Stool cultures were positive for Salmonella in another 4 cases (8, 10, 11, 12). In the other 3 cases (7, 9, 13), the diagnosis relied on history of simultaneous diarrhoea and arthritis and exclusion of all other possibilities such as ulcerative colitis and regional enteritis.

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This group represented the 'reactive arthritis' and served for comparison in the tissue typing. 2 of these patients (9, 10) had a typical Reiter's syndrome with arthritis, conjunctivitis, and urethritis preceded by an episode of diarrhoea.

Most of these arthritides were transient. Those associated with rubella and other viruses tended to be of short duration and to be followed by full recovery without residua. By contrast, those that followed dysentery tended to last longer, and at least one patient has progressed to definite sacroiliitis.

Method

Lymphocyte typing was carried out at the Tissue Typing Laboratory, Westminster Hospital, using a modified two stage lymphocytotoxicity micromethod (Terasaki and McClelland, 1964) testing the patients and controls for 23 antigens. A code was used instead of a diagnosis when this test was requested in order to avoid technical bias.

Results (Table I)

Only 13% of patients with presumed rubella arthropathy possessed the antigen B27. The number of cases (23) is small but one may already see a lack of strong association in this condition. The group of arthritis associated with different virus infections showed that 29% (5/17) of these cases possessed B27. This antigen was found in one of the 2 cases of mumps and in 4 of the 9 patients whose only laboratory anomaly was a leucopenia with or without increased sedimentation rate. By contrast, 92% of patients (12/13) with arthritis following an episode of diarrhoea had the antigen B27. The only exception was a young Italian boy with a typical Reiter's syndrome following severe dysentery.

Discussion

The identification of Shigella as a cause of Reiter's syndrome (Noer, 1966), and of Salmonella, Shigella, and Yersinia as a cause of sacroiliitis (Aho and others, 1975), added to their respective strong association with B27, gave a new perspective in the study of rheumatic diseases.

Ankylosing spondylitis has nearly become the hallmark of B27 (Caffrey and James, 1973). Ulcerative colitis, regional enteritis, and psoriasis, if complicated by a spondylitis and only then (Brewerton and others, 1974), seem strongly associated with this same antigen. On the other hand, conditions such as reactive arthritis, acute anterior uveitis, balanitis, keratodermia blennorrhagica are associated with B27 without necessarily having a spinal involvement. It was therefore of interest to search for a genetic marker in arthritis associated with other infections, even when spinal manifestations are not usual.

Not only is there no significant increased frequency of B27 (13%) in rubella arthritis, there is no evidence of any other abnormal HLA association. The group of mixed viral infection (Table II) is more difficult to evaluate as there are insufficient numbers in any one subgroup. It is worth noting that the increased incidence of HLA-B27 appears to arise from those subjects with no identified aetiology for their arthropathy and leucopenia. However, a genetic cause is at least partly responsible for the expression of certain forms of arthritis, as shown by Aho in his studies of reactive arthritis following infection which showed a strong linkage with B27. The present work confirms these findings. Further progress in the elucidation of the HLA complex will most likely give much more information about these associations and their significance.

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Table I *Occurrence of HLA-B27*

Groups of patients	*B-27(%)*	*No.*
Presumed rubella arthritis	13	3/23
Mixed viral arthritis	29	5/17
Dysentery associated arthritis	92	12/13
Controls	8	48/600

Table II *Group of mixed viral arthritis*

Case no.	*Associated features*	*HLA complex*	
		Locus A	*Locus B*
1	Clinical mumps	2, W29	12, 27
2	Clinical mumps	— —	5, W10
3	Clinical glandular fever	2, 3	12, —
4	Clinical glandular fever	3, 10	8, W15
5	Clinical glandular fever	1, 3	7, 8
6	Parainfluenza titre increased	2, 9	12, —
7	Cytomegalic virus titre increased	1, W29	7, 8
8	Respiratory syncytial cell titre increased	2, —	12, 17
9	Transient leucopenia; ESR raised	1, 2	8, 27
10	Transient leucopenia; ESR raised	3, —	—, 27
11	Transient leucopenia; ESR raised	2, 9	12, 14
12	Transient leucopenia	2, 9	12, 27
13	Transient leucopenia	1, —	—, 27
14	Transient leucopenia	2, 3	7, 12
15	Hx of rubella; no contact; serology negative	1, 2	8, 14
16	Serology negative; ESR raised	9, —	7, —
17	Serology negative; ESR raised	1, 3	7, 8

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