

Significance of rubella virus infection in juvenile chronic polyarthritis

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SUMMARY Fifty-three patients under the age of 5 years with definite juvenile chronic polyarthritis (JCP) were examined for serological evidence of rubella infection. The prevalence of rubella antibody was found to be low and did not differ significantly from that found in normal children of similar age. Patients with JCP and antibody to rubella virus had a clinical course indistinguishable from those with no detectable rubella antibody.

The role of viruses in the aetiology and pathogenesis of connective tissue diseases has been widely discussed (Phillips, 1971; Marmion, 1974; Denman, 1975) but definitive data to confirm such a relationship are lacking. Rubella virus has often been proposed to be of aetiological significance, particularly in juvenile chronic polyarthritis (JCP). Sero-epidemiological data (Ogra and Herd, 1972; Deinhard *et al.*, 1974; Ogra *et al.*, 1975) and the finding of both a heightened and prolonged antibody response to rubella infection in patients with JCP (Ogra *et al.*, 1975) has recently provided more direct evidence for a possible role of rubella virus in JCP.

An outbreak of rubella which occurred among our hospitalized patients with JCP presented the opportunity to examine the manner in which these patients responded to naturally acquired infection by this agent. The results of that investigation (Howard *et al.*, 1975), while confirming the heightened serological response noted by some (Ogra and Herd, 1972; Ogra *et al.*, 1975) but not all investigators in patients with JCP, stimulated the present study to determine the importance of rubella virus in the aetiology and pathogenesis of JCP. If rubella were an important aetiological agent in a substantial number of children with JCP, a higher incidence of rubella antibody among children with JCP might be expected to be found compared to the normal population. Any

difference between these populations in frequency of antibody to rubella would best be appreciated by studying the youngest age groups as children acquire rubella infection in an age-dependent manner and thus antibody to rubella virus is infrequently found under the age of 5 years (Dudgeon *et al.*, 1973).

Patients and methods

Between January 1970 and December 1975, 68 children under the age of 5 years were referred to the MRC Rheumatism Unit at Taplow with definite JCP (Ansell and Bywaters, 1962). Of these, 53 had a serum sample taken before their fifth birthday which was available for study. No difference in type or age of onset, sex, or subsequent course was found between those patients studied and the 15 children for whom a serum sample was not available. The control population consisted of children attending an outpatient clinic from whom blood samples were being collected for other purposes. None of these children had manifestations of congenital rubella.

Antibody to rubella virus was detected by means of the haemagglutinin-inhibiting (HI) antibody test as has been previously described (Marshall *et al.*, 1971). Sera with HI titres of 1:8 or greater were considered positive. Complement-fixing antibody tests were performed in microtitre plates using a modification of the method described by Bradstreet and Taylor (1962). Antigens for the complement-fixation tests were kindly supplied by Dr. P. Bradstreet, Standards Laboratory, Central Public Health Laboratory, Colindale.

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Results

The prevalence of rubella HI antibody among the 53 patients with JCP is shown in the Table. The prevalence was low in all age groups. The percentage of children up to the age of 4 with rubella antibody closely paralleled the data for the control population. A diminished prevalence of rubella antibody was noted in the oldest JCP age group sampled (4–5 years); this difference is not significant ($P > 0.20$) and may be due to the limited sample size. The titres of HI antibody in the 6 children who were seropositive ranged from 1:16 to 1:256 (geometric mean titre 45.3).

Table Prevalence of rubella HI antibody in JCP and control children

Children	Age (yr)			
	1	2	3	4
JCP	0/2 (0%)	1/9 (11%)	3/20 (15%)	2/22 (9%)
Control	2/73 (2.7%)	5/81 (6.1%)	10/78 (13%)	11/57 (19%)

Comparison of the 6 JCP children with rubella antibody to the remaining 47 children failed to show any differences in age or type of onset of JCP, sex, number of joints involved, presence of autoantibodies to DNA or smooth muscle, history of prior vaccination (DPT, vaccinia, polio, rubella), or clinical history of childhood diseases, including rubella. The subsequent course of the disease, during follow-up ranging from 6 months to 6½ years, likewise appeared to be no different in the two groups.

Other serological data obtained in the entire group of patients showed complement-fixing antibodies to adenovirus (61% of patients), herpes simplex (40%), influenza A and B (26% and 28% respectively), measles (57%), mumps (59%), and mycoplasma pneumonia (53%).

Discussion

As the great majority of young patients with definite JCP have been shown to have no serological evidence of rubella infection, it seems unlikely that this agent is of aetiological significance in JCP. Any further theories attempting to implicate rubella in the aetiology of JCP, to be consistent with these findings, would have to invoke a specific immunological hyporesponsiveness to primary rubella infection in almost all children destined to develop JCP. The fact that patients with JCP who do not have detectable antibody to rubella can be infected in a

normal fashion by this virus (Ogra *et al.*, 1975; Linnemann *et al.*, 1975) and that their serological response occurs with an antibody pattern typical of a primary rather than a secondary response (Linnemann *et al.*, 1975; Al-Nakib *et al.*, 1975; Pattison, 1975) makes the existence of such an immunological abnormality unlikely.

The high incidence reported by Ogra *et al.* (1975) of rubella antigen present in synovial cells of patients with JCP and the general findings of heightened IgG and persistent levels of IgM rubella antibody in patients with JCP (Ogra *et al.*, 1975) raise the possibility that rubella infection of patients with pre-existing JCP may commonly result in persistence of this viral agent. Cartilage (Smith *et al.*, 1973) and synovial tissue (Parker *et al.*, 1972) have both been shown to be capable of supporting multiplication of rubella virus. If these tissues manifest increased susceptibility to persistent or chronic rubella infection as a consequence of involvement by the pathological process of JCP, an explanation would be provided for both the heightened antibody response, comparable to that of patients with proven rubella arthritis (Ogra *et al.*, 1975), and the finding of rubella antigen in cells from the joints of patients with JCP.

This hypothesis, while supported by indirect evidence including the demonstration of a relationship between the extent of joint involvement and the magnitude of the rubella antibody titre (Cassidy *et al.*, 1974) and the finding of normal rather than raised rubella antibody titres in patients who develop JCP later in life after acquiring rubella infection (Lerman *et al.*, 1971), is also amenable to direct testing. It would be expected that rubella virus, as well as rubella antigen, should be detectable in the joints of patients with JCP at the time they develop clinical rubella infection. A systematic examination for the presence of rubella virus in the joints of such patients has not yet been made, and in the single case reported (Ogra and Herd, 1971) the presence of neutralizing antibody may have prevented recovery of the virus. However, as patients with JCP undoubtedly either acquire natural rubella or will be vaccinated with live rubella virus, it should be feasible to determine whether joint infection and viral persistence are common accompaniments of rubella infection in this population.

Rahal *et al.* (1976) have recently presented data supporting a causal relationship between preceding common viral infections and the development of nonspecific febrile arthritis. They have also suggested that in some instances such infections might be related to the development of juvenile rheumatoid arthritis. However, the serological data in this group of JCP patients failed to show evidence of a strikingly

high incidence of previous infection with other common viral agents.

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