Clin. exp. Immunol. (1970) **6**, 885–889.

A STUDY OF RUBELLA HAEMAGGLUTINATION INHIBITION ANTIBODIES IN RHEUMATOID ARTHRITIS

J. N. KACAKI, P. C. BALDUZZI AND J. H. VAUGHAN

Departments of Medicine and Microbiology, The University of Rochester School of Medicine and Dentistry, Rochester, New York

(*Received* 16 *December* 1969)

SUMMARY

In the literature there are speculations concerning a possible role of Rubella virus in the etiopathogenesis of rheumatoid arthritis (RA). Rubella haemagglutination inhibition (RHI) antibody titres were determined in sera from thirty-six pairs of patients with RA and diseases unrelated to RA, matched for age and sex. Latex flocculation tests (LFT) were performed in both groups, as well. Mean ranks ($\log_2$) of RHI test for the RA and non-RA groups were almost identical (5·75 and 5·94, respectively). Titre of RHI was unrelated to the presence or absence, or titre, of LFT. Thus, no evidence of continuing Rubella virus infection can be found in patients with RA by this antibody test. The possibility that the aetiology of RA may be related to some viral infection is nevertheless of continuing interest.

INTRODUCTION

The onset of rheumatoid arthritis (RA) and exacerbations of known cases may occur after infections (Robinson, 1966), and a viral aetiology of the disease has been considered (Holland *et al.*, 1962). Polyarthritis occurring after Rubella infections and vaccination resembles RA in clinical appearance (Geiger, 1918; Weibel *et al.*, 1969). However, it has been generally considered as a clinical entity separate from RA (Chambers & Bywaters, 1963; Kantor & Tanner, 1962). Johnson & Hall (1958) noted the high incidence of positive latex flocculation tests (LFT) in a group of patients with Rubella arthritis and suggested that such cases 'may afford an opportunity to isolate a virus of causative importance in rheumatoid arthritis'. In a recent, detailed report of a case of RA developing after Rubella, Martenis, Bland & Phillips (1968) suggested again that Rubella virus may have played a role in the etiology of RA.

The present study of Rubella haemagglutination inhibition (RHI) antibodies in sera of patients with RA and unrelated conditions was performed on the assumption that if there were a causative relationship between Rubella virus and RA, some difference in RHI titres should be found between the two groups of sera.

Correspondence: Dr John H. Vaughan, Department of Medicine, 260 Crittenden Boulevard, Rochester, New York 14620, U.S.A.

TABLE 1

Pair	Sex	RA group			Non-RA group			Diagnosis
		Age	Rank RHI	Rank LFT	Age	Rank RHI	Rank LFT	
1	F	14	6	0	13	10	0	Nephritis
2	M	17	0	4	18	7	0	Seizures
3	F	21	4	0	21	5	0	DM
4	F	27	10	6	27	6	0	Ataxia
5	F	30	8	0	30	9	0	Craniotomy
6	F	31	0	0	31	6	0	PID
7	F	43	7	5	43	8	0	DM
8	M	43	6	5	44	6	0	Nephritis
9	F	44	7	7	46	8	0	CHF
10	F	44	8	5	46	8	0	DA
11	F	46	4	4	47	4	0	DM
12	F	48	9	0	49	5	0	Weight loss
13	M	49	5	8	48	4	0	CHF
14	F	51	5	0	52	3	0	PMI
15	F	54	7	3	54	7	0	DA
16	F	54	8	0	54	10	0	CHF
17	F	55	6	8	52	1	0	PI
18	M	56	3	8	52	7	0	Hypertension
19	F	57	5	3	56	8	0	PMI
20	M	57	4	6	58	4	3	MI
21	F	60	5	0	61	3	0	Hypothyroid
22	F	60	6	8	61	5	8	Anaemia
23	F	61	4	8	61	6	0	DA
24	M	61	7	8	62	3	8	DA
25	M	63	7	8	60	0	0	MI
26	F	63	8	6	66	5	0	CHF
27	F	63	4	2	62	6	1	MI
28	F	64	7	5	65	10	8	CHF
29	M	65	10	0	64	6	0	MI
30	F	68	9	2	67	5	N.D.	DA
31	M	68	4	6	67	1	0	Anaemia
32	M	69	6	8	70	10	5	MI
33	F	69	8	0	68	9	0	Hypothyroid
34	F	70	4	0	71	5	4	DA
35	F	72	4	8	71	7	0	Hyperthyroid
36	F	72	3	8	67	7	0	CHF
Total	26 F 10 M							
Means		52·5	5·7	4·1	52·3	5·9	1·0	

CHF: congestive heart failure. DA: degenerative arthritis. DM: diabetes mellitus. MI: myocardial infarction. PI: pulmonary infiltration. PID: pelvic inflammatory disease. PMI: possible myocardial infarction.

METHODS

The sera examined had all been received at this laboratory for determination of immunoglobulin, complement, or autoantibody contents during a one year period. Thirty-six sera from patients with diseases other than those of the connective tissue were chosen for this investigation. These sera were then matched for age and sex with thirty-six sera from RA patients from the same serum bank. Twenty-five of the RA sera were seropositive by LFT and 11 were seronegative.

The RHI test was performed by the method of Stewart *et al.* (1967). Rubella HA antigen was obtained from Flow Laboratories, Inc. Sera were titrated blindly, the diagnostic categories being revealed only after the RHI titres had been read. The RHI titres ranged from $<1/8$ to 1/4096 and were ranked 0–10 by their $\log_2$ values beginning with $1/8 = 1$. LFT test was performed by the method of Singer & Plotz (1956). The titres ranged from $<1/40$ to 1/5120 and were ranked 0–8 with $1/40 = 1$.

RESULTS

The results are shown in Table 1 and Fig. 1. The mean age in the RA group was 52·5 and in the non-RA 52·3 years. The mean ranks of RHI titres were 5·75 for the RA group and 5·94 for the non-RA group. These ranks were not significantly different by χ^2 test. No

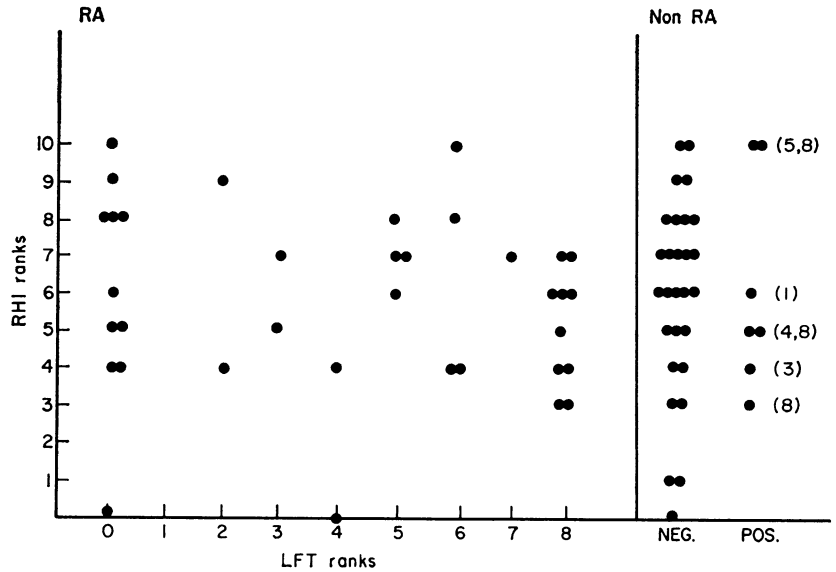

FIG. 1. Lack of relation of Rubella antibody titre (RHI) to anti-γG titre (rheumatoid factor, LFT) in patients with rheumatoid arthritis or non-rheumatoid disease. The ranks ($\log_2$) of titres of LFT are given on the abscissa for the RA group and in parentheses for the non-RA group.

difference in RHI titres was found within the RA group between latex positive (mean 5·64) and negative sera (mean 6·09) or between RA latex positive (mean 5·64) and their matched non-RA sera (mean 5·48). The titre of RHI was unrelated to the titre of LFT in LFT-positive sera. The difference of ranks of latex titres between the RA and the non-RA groups was highly significant ($P<0·001$).

DISCUSSION

Johnson & Hall (1958) studied the LFT inhibition test in cases of Rubella with and without complicating arthritis. They found that this test gave positive reactions in nine out of ten cases with arthritis, but in only two out of seven cases without arthritis. These results led them to suggest that a possible relationship existed between Rubella virus and rheumatoid arthritis. Riddell (1962) briefly reported one patient with Rubella arthritis in whom the joint disease continued to progress until it exhibited features typical of RA, but presented no clinical or laboratory documentation.

Martenis, Bland & Philips (1968) described a case of a 21-year-old woman who developed RA immediately following Rubella arthritis. Her serum converted from negative latex and sheep cell agglutination reactions to strongly positive reactions in a short period. The patient was followed for over 5 years, maintained the positivity in the latex and sheep cell tests, as well as high RHI titres and Rubella neutralizing and complement fixing antibodies. The authors felt that such a prolonged maintenance of high titres of RHI antibodies was consistent with repeated or continued exogenous or endogenous exposure to Rubella virus, uggesting that this virus may have played some role in the aetiology of RA.

Kantor & Tanner (1962), on the other hand, carried out a prospective study of fourteen patients with Rubella arthritis. During an observation period lasting 2–5 years, none of their patients developed RA, nor did any develop anti-IgG antibodies, although one had a positive sheep cell agglutination inhibition test initially.

In the present study, we have found that selected sera of patients with RA were indistinguishable in their RHI antibody titres from matched sera of patients with diseases unrelated to RA. Furthermore, there was no correlation between titres of LFT and titres of RHI. While we take this finding to mean that there is probably no causal relation between Rubella infection and rheumatoid arthritis, it must be admitted that we have not ruled out the possibility that the virus may act like a slow virus (Rawls, 1968), infecting without eliciting a significant antibody response. Rubella is known presently, however, to cause only acute self-limited infection or, in congenital cases, chronic infection with large quantities of virus excreted and high titres of antibody (Plotkin, Cochran & Lindquist, 1967).

We believe our observations add substantially to the negative findings of Kantor & Tanner (1962). The possibility that the etiology of RA may be related to some viral infection is of continuing interest, but Rubella virus does not seem to be the best candidate.

ACKNOWLEDGMENTS

Supported by a Fellowship Grant from the Monroe County Chapter of the Arthritis Foundation through the Community Chest and Grants AM-02443 and AI-28 from the National Institutes of Health, Bethesda, Maryland.

The technical assistance of Mrs Doris Kreckman is gratefully acknowledged.

REFERENCES

CHAMBERS, R.J. & BYWATERS, E.G.L. (1963) Rubella synovitis. *Ann. rheum. Dis.* **22,** 263.

GEIGER, J.C. (1918) Epidemic of German measles in city adjacent to Army cantonment: and its probable relation thereto. *J. Amer. med. Ass.* **70,** 1818.

HOLLANDER, J.L., BROWN, E.M., JR, JESSAR, R.A., HUMMELER, K. & HENLE, W. (1962) Studies on relationship of virus infections to early or acute rheumatoid arthritis. *Arch. Inter-Amer. Rheum.* (*Rio de Janeiro*), **5,** 137.

JOHNSON, R.E. & HALL, A.P. (1958) Rubella arthritis. Report of cases studied by latex test. *New Engl. J. Med.* **258,** 743.

KANTOR, T.G. & TANNER, M. (1962) Rubella arthritis and rheumatoid arthritis. *Arthr. and Rheum.* **5,** 378.

MARTENIS, T.W., BLAND, J.H. & PHILLIPS, C.A. (1968) Rheumatoid arthritis after rubella. *Arthr. and Rheum.* **11,** 683.

PLOTKIN, S.A., COCHRAN, W. & LINDQUIST, J.M. (1967) Congenital rubella syndrome in late infancy. *J. Amer. med. Ass.* **200,** 435.

RAWLS, W.W. (1968) Congenital rubella: The significance of virus persistence. In *Progress in Medical Virology* (Ed. by J. L. Melnick), 10th edn, p. 238. Karger, Basel.

RIDDELL, L.A. (1962) Arthritis and rubella. *Brit. med. J.* **1,** 1076.

ROBINSON, W. (1966) The etiology of rheumatoid arthritis. In *Arthritis and Allied Conditions.* (Ed. by J. Hollander), 7th ed., p. 182. Lea & Febiger, Philadelphia.

SINGER, J.M. & PLOTZ, C.M. (1956) The latex fixation test. I. Application to serologic diagnosis of rheumatoid arthritis. *Amer. J. Med.* **21,** 888.

STEWART, G.L., PARKMAN, P.D., HOPPS, H.E., DOUGLAS, R.D., HAMILTON, J.P. & MAYER, H.J., JR (1967) Rubella virus hemagglutination-inhibition test. *New Engl. J. Med.* **276,** 554.

WEIBEL, R.R., STOKES, J., JR, BUYNAK, E.B. & HILLEMAN, M.R. (1969) Rubella vaccination in adult females. *New Engl. J. Med.* **280,** 682.

ABBREVIATIONS

LFT, latex fixation test

RHI, Rubella haemagglutination inhibition