

Serum immunoglobulin and β_{1C}/β_{1A} globulin concentrations in juvenile rheumatoid arthritis

K. M. GOEL, R. W. LOGAN, W. P. BARNARD, AND R. A. SHANKS

From the Departments of Child Health and Biochemistry, Royal Hospital for Sick Children, Glasgow, G3 8SJ

Alterations in the type and concentration of serum immunoglobulins in patients with rheumatoid arthritis have been reported by several authors (Mackiewicz and Fenrych, 1961; Cassidy and Burt, 1967; Veys and Claessens, 1968; Houba and Bardfeld, 1969). So, too, the complement activity of serum and synovial fluid in rheumatoid arthritis has recently been studied in adults and to a lesser extent in children (Muller and Muller-von Voigt, 1968; Wasastjerna and Ekelund, 1969; Weinstein, Peters, Brown, and Bluestone, 1972). Conflicting results have been reported by these authors and the purpose of this paper is to report a further study of immunoglobulin changes in this disease.

The present study was planned during the long-term follow-up study of patients with juvenile rheumatoid arthritis (JRA). The concentrations of immunoglobulins (IgA, IgG, and IgM), β_{1C}/β_{1A} globulins and rheumatoid factor (Waalser-Rose and latex-fixation tests) in serum were estimated. The values of the four globulins in patients with three modes of onset of JRA have been compared. An attempt was also made to find a possible correlation between these parameters and the clinical state or course of the disease.

Material and methods

Serum was obtained from 79 patients with JRA who satisfied the diagnostic criteria of Ansell and Bywaters (1959). Immunoglobulin and β_{1C}/β_{1A} globulin concentrations were estimated by a Mancini technique as previously described (Carswell and Logan, 1973). The Waalser-Rose test was performed by the method of Greenbury (1957) and latex-fixation by Hyland RA-test (Hyland Laboratory, California, U.S.A.).

Of these 79 patients, a radiological survey was performed in fifty cases at the time of reassessment. The radiological changes were classified into one of the five categories according to the criteria of Kellgren and Lawrence (1957).

We have classified our cases with JRA or Still's diseases into three major clinical subgroups, according to the mode

of onset of their symptoms. Those patients in whom the onset was acute with primarily systemic manifestations (fever, typical rash, splenomegaly, lymphadenopathy, leucocytosis, neck involvement, and arthralgia), have been termed early-onset JRA, as they tended to occur in younger children in spite of an overlap in age distribution with those we termed late-onset JRA. The mean age at onset of symptoms for the early-onset group was 4½ years. This is the type which other authors have described as classical Still's disease or infantile type JRA (Calabro and Marchesano, 1968; Robinson, 1969).

Those with insidious onset, polyarthritis, and few systemic features have been grouped as late-onset JRA (labelled 'adult type' or polyarticular-onset JRA by Calabro and Marchesano, 1968; Robinson, 1969), and those with single joint involvement as monoarticular-onset JRA. The mean age at onset of symptoms for late-onset JRA was 9½ years and for monoarticular-onset JRA it was 4½ years.

Of the 79 cases, thirty were of early-onset, 41 of late-onset, and eight of monoarticular-onset. Of these, 69 were in remission while ten had active rheumatoid disease, and in the active group, four were of early-onset and six of late-onset. In none of the patients with monoarticular arthritis was the disease active.

The mean duration of the disease at the time of the study was 10 years 1 month.

The functional status of the 79 patients has been grouped into the grades described by Goel and Shanks (1974).

Results

In Tables I and II is shown the significance of the results when compared in groups with normal mean values and individually with appropriate normal ranges.

None of the patients had subnormal immunoglobulin results with the exception of one who developed late-onset JRA 4 years after the diagnosis of Bruton's hypogammaglobulinaemia.

Table III shows those groups where the active form of the disease was associated with a greater concentration of globulins than found in the inactive form.

Table I Significance of differences between results from normal subjects and 79 patients with juvenile rheumatoid arthritis

Type of JRA	No. of patients	IgA	IgG	IgM	β_{1C}/β_{1A}
Early-onset	30	135.8 P = 0.025	155.1 P < 0.01	170.5 P < 0.01	116.6 P = 0.03
Late-onset	41	126.2 P = 0.02	159.7 P < 0.01	173.6 P < 0.01	120.2 P = 0.02
Mono-articular	8	113.4 N.S.	130.6 P = 0.02	150.5 P < 0.01	109.9 N.S.

For each group, the mean of the results from the rheumatoid patients is expressed as a percentage of normal and the probability of the group differing from normal purely by chance is also shown. N.S. = not significant (P > 0.10).

Table II Immunoglobulin, β_{1C}/β_{1A} globulin, Waaler-Rose and latex-fixation results in juvenile rheumatoid arthritis

Type of JRA	No. of patients	IgA			IgG			IgM			β_{1C}/β_{1A}			Waaler-Rose and latex-fixation
		L	N	H	L	N	H	L	N	H	L	N	H	
Early-onset	30	0	80	20	0	60	40	0	56.7	43.3	0	86.7	13.3	Negative
Late-onset	41	2.4	78.0	19.6	2.4	46.3	51.3	0	48.7	51.3	0	85.4	14.6	Negative
Mon-articular	8	0	87.5	12.5	0	87.5	12.5	0	75	25	0	87.5	12.5	Negative

The results shown are percentage patients for each of the types concerned. L = Subnormal, N = Normal, H = Increased.

Table III Significance of differences between results observed in the active and inactive forms of juvenile rheumatoid arthritis

Type of JRA	No. of patients	IgA	IgG	IgM	β_{1C}/β_{1A}
Early-onset Inactive	30	N.S.	P < 0.01*	N.S.	N.S.
Early-onset Active					
Late-onset Inactive	41	P < 0.05*	P < 0.01*	N.S.	N.S.
Late-onset Active					

N.S. = Not significant (P > 0.10).
* Active greater.

A comparison of the immunoglobulin and β_{1C}/β_{1A} globulin results in patients with the three varieties of JRA showed that there were no significant differences (P > 0.10) within respective classes between any of the results in the groups concerned. So, too,

the results in the active forms of early- and late-onset JRA did not differ.

Table IV shows the comparison of immunoglobulin and β_{1C}/β_{1A} globulin results with radiological findings.

Table IV Comparison of immunoglobulin, β_{1C}/β_{1A} globulin, and radiological findings

Immunoglobulin	Status	No.	Radiological grade				P
			None or Mild (I)		Moderate or Severe (II)		
IgA	Increased	7	2	5	0.05 > P > 0.02		
	Normal	43	31	12			
IgG	Increased	19	6	13	0.02 > P > 0.01		
	Normal	31	27	4			
IgM	Increased	24	12	12	0.05 > P > 0.02		
	Normal	26	21	5			
β_{1C}/β_{1A} globulins	Increased	10	5	5	0.50 > P > 0.20		
	Normal	40	28	12			

A systematic attempt was also made to compare the current functional status of the patient and the clinical course of the disease (monocyclic, intermittent, continuous) with the immunoglobulin and β_{1C}/β_{1A} globulin results. No useful relationships could be demonstrated.

Discussion

In our study we have found raised IgG and IgM values in a high proportion of patients with both early- and late-onset JRA.

IgA values were also noted to be increased but only in a small number of patients. Veys and Claessens (1968) reported raised IgG and IgA levels in their series but they did not find statistically significant differences between IgM levels in normal subjects and rheumatoid patients. These authors postulated that the increase in serum IgG in rheumatoid arthritis was due to the presence of constant antigenic stimulation. In contrast, Mackiewicz and Fenrych (1961) found elevated IgM values in most of their cases of rheumatoid arthritis.

Cassidy and Burt (1967) reported selective IgA deficiency in their patients with JRA apart from the known increased incidence of arthritis in classical forms of hypo- and dysgammaglobulinaemia. We found subnormal immunoglobulin levels in only one patient with late-onset JRA (a case of Bruton's type hypogammaglobulinaemia with subnormal IgA and IgG results).

Although we found elevated levels of IgM in all three types of JRA, the Waaler-Rose and latex-fixation tests were negative in all cases. This could be explained by the fact that the Waaler-Rose and latex-fixation tests involve only a fraction of the IgM immunoglobulins. Other authors have also failed to find a direct correlation between IgM values and the presence or absence of rheumatoid factor in the serum of patients with rheumatoid arthritis (Claman and Merrill, 1966; Barden, Mullinax, and Waller, 1967; Marcolongo, Carcassi, Frullini, Bianco, and Bravi, 1967).

Our results show, however, that disease activity is associated with the elevation of IgG values.

There have been conflicting reports in the literature on β_{1C} globulin content in adult rheumatoid arthritis patients. Muller and Muller-von Voigt (1968) reported that the β_{1C}/β_{1A} globulin content in the sera of their patients was higher but the difference was not statistically significant. However, recently, Franco and Schur (1971) reported low levels of serum complement in more severe forms of adult rheumatoid arthritis.

In this study we have demonstrated a statistically significant increase in β_{1C}/β_{1A} values in both early- and late-onset JRA patients. It was noted that there was no correlation between the β_{1C} globulin and the

disease activity. None of our patients had subnormal complement levels.

Despite variable levels of complement in the serum of adult rheumatoid patients, low levels have been found consistently in adult rheumatoid synovial fluids, with one report of similar results in children, and more recently degradation products of complement (C_3) have been demonstrated in synovial fluid (Schubart, Ewald, Schroeder, Rothschild, Bhatavadekar, and Pullen, 1965; Pekin and Zvaifler, 1962; Hedberg, Lundh, and Laurell, 1970). It is possible, therefore, that there could be an increased intra-articular consumption of complement in rheumatoid arthritis, despite the normal or elevated serum complement levels in this disease (Weinstein, Peters, Brown, and Bluestone, 1972).

Similarly, Wasastjerna and Ekelund (1969) have reported that the influence on the levels of circulating globulins cannot be predicted, as an increased consumption is probably followed by an increased production, and the combined effect may be high, normal, or low levels. This could perhaps help to explain the conflicting results in various series.

Patients with increased immunoglobulins showed a significantly higher incidence of moderate or severe radiological changes, although no particular joint was consistently involved. No significant association was found between the radiological grade and β_{1C}/β_{1A} globulin concentrations.

It would appear from the present study that, in the individual patient, neither serum immunoglobulin nor β_{1C}/β_{1A} globulin concentrations have any diagnostic or prognostic significance.

Summary

Serum IgA, IgG, IgM, and β_{1C}/β_{1A} globulin estimations and tests for rheumatoid factor (Waaler-Rose and latex-fixation) were performed in 79 patients with juvenile rheumatoid arthritis (JRA).

Clinically, the patients were classified into three groups: those with early-onset, late-onset, and monoarticular-onset arthritis. Mean values of IgG and IgM were found to be elevated in all three types of JRA. The elevation of mean IgA concentration was significant only in the early- and late-onset groups.

IgG concentrations were significantly higher in the active forms of both early- and late-onset JRA patients, while IgA was greater only in the active form of late-onset JRA.

β_{1C}/β_{1A} globulin was higher than normal only in early- and late-onset groups. Disease activity did not influence complement concentration and none of the patients had subnormal levels.

The Waaler-Rose and latex-fixation tests were negative in all 79 patients (whether active or inactive)

although rheumatoid factor is said to be associated with the IgM class of globulins.

A comparison of the severity of radiological changes with immunoglobulin concentrations revealed a positive correlation. This did not apply to the β_{1C}/β_{1A} globulin results.

No correlation was found between the immuno-

globulin or β_{1C}/β_{1A} globulin concentrations and the severity or clinical course of the disease.

We are grateful to our colleagues for allowing us to study patients under their care. The rheumatoid serology was kindly performed by the Department of Bacteriology and Immunology of the Western Infirmary, Glasgow.

References

- ANSELL, B. M., AND BYWATERS, E. G. L. (1959) *Bull. rheum. Dis.*, **9**, 189 (Prognosis in Still's disease)
- BARDEN, J., MULLINAX, F., AND WALLER, M. (1967) *Arthr. and Rheum.*, **10**, 228 (Immunoglobulin levels in rheumatoid arthritis: comparison with rheumatoid factor titers, clinical stage and disease duration)
- CALABRO, J. J., AND MARCHESANO, J. M. (1968) *Med. Clin. N. Amer.*, **52**, 567 (The early natural history of juvenile rheumatoid arthritis)
- CARSWELL, F., AND LOGAN, R. W. (1973) *Arch. Dis. Childh.*, **48**, 587 (Plasma concentrations of β_{1C}/β_{1A} globulins and immunoglobulins in children with untreated coeliac disease)
- CASSIDY, J. T., AND BURT, A. (1967) *Arthr. and Rheum.*, **10**, 272 (Isolated IgA deficiency in juvenile rheumatoid arthritis)
- CLAMAN, H. N., AND MERRILL, D. (1966) *J. Lab. clin. Med.*, **67**, 850 (Serum immunoglobulins in rheumatoid arthritis)
- FRANCO, A. E., AND SCHUR, P. H. (1971) *Arthr. and Rheum.*, **14**, 231 (Hypocomplementemia in rheumatoid arthritis)
- GOEL, K. M., AND SHANKS, R. A. (1974) *Ann. rheum. Dis.*, **33**, 25 (A follow-up study of 100 cases of juvenile rheumatoid arthritis)
- GREENBURY, C. L. (1957) 'The Waaler-Rose Test'. Association of Clinical Pathologists Broad Sheet No. 18 (New Series). B.M.A., London
- HEDBERG, H., LUNDH, B., AND LAURELL, A. B. (1970) *Clin. exp. Immunol.*, **6**, 707 (Studies of the third component of complement in synovial fluid from arthritic patients)
- HOUBA, V., AND BARDFELD, R. (1969) *Ann. rheum. Dis.*, **28**, 55 (Serum immunoglobulins in juvenile rheumatoid arthritis)
- KELLGREN, J. H., AND LAWRENCE, J. S. (1957) *Ibid.*, **16**, 485 (Radiological assessment of rheumatoid arthritis)
- MACKIEWICZ, S., AND FENRYCH, W. (1961) *Ibid.*, **20**, 265 (Immuno-electrophoretic analysis of proteins in serum and synovial fluid in rheumatoid arthritis and ankylosing spondylitis)
- MARCOLONGO, R., JR., CARCASSI, A., FRULLINI, F., BIANCO, G., AND BRAVI, A. (1967) *Ibid.*, **26**, 412 (Levels of serum immunoglobulins in patients with rheumatoid arthritis)
- MULLER, H. E., AND MULLER-VON VOIGT, I. (1968) *Dtsch. med. Wschr.*, **93**, 216 (Quantitativ immunologische Serumproteinbestimmungen bei verschiedenen Krankheitszustanden)
- PEKIN, T. J., AND ZVAIFLER, N. J. (1962) *Arthr. and Rheum.*, **5**, 314 (Measurement of haemolytic complement in synovial fluids)
- ROBINSON, M. J. (1969) *Aust. paediat. J.*, **5**, 155 (Rheumatoid arthritis in childhood: A study of 60 cases)
- SCHUBART, A. F., EWALD, R. W., SCHROEDER, W. C., ROTHSCHILD, H. J., BHATAVADEKAR, D. N., AND PULLEN, P. K. (1965) *Ann. rheum. Dis.*, **24**, 439 (Serum complement levels in rheumatoid arthritis)
- VEYS, E. M., AND CLAESSENS, H. E. (1968) *Ibid.*, **27**, 431 (Serum levels of IgG, IgM, and IgA in rheumatoid arthritis)
- WASASTJERNA, C., AND EKELUND, P. (1969) *Acta med. scand.*, **186**, 469 (The serum immunoglobulin and β_{1C}/β_{1A} globulin levels in rheumatoid arthritis)
- WEINSTEIN, A., PETERS, K., BROWN, D., AND BLUESTONE, R. (1972) *Arthr. and Rheum.*, **15**, 49 (Metabolism of the third component of complement (C_3) in patients with rheumatoid arthritis)