Immunoglobulins and Complement Components in Synovial Fluid of Patients with Acute Rheumatic Fever

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ABSTRACT Three components of complement and six other serum proteins were assayed in synovial fluid and serum samples from 25 patients with acute rheumatic fever in Trinidad. The resulting data indicate a relative decrease in both early and late components of complement within the synovial fluids which suggests local activation by immune complexes. Such activation of complement within the joint spaces may play a primary role in development of the inflammatory arthritis of acute rheumatic fever.

INTRODUCTION

Migratory polyarthritis is a common clinical feature of acute rheumatic fever (ARF)[1] and is one of the major criteria for its diagnosis (1). The pathogenesis of the polyarthritis remains unknown although its relation to preceding group A streptococcal infections has been well established. While the role of complement has been investigated in several other rheumatic diseases (2–7), its status in the arthritis associated with ARF has not been described. In both rheumatoid arthritis and juvenile rheumatoid arthritis, depletion of complement within synovial fluid has been related to the presence of immune complexes and the severity of the arthritis. In the present study, therefore, we examined the status of complement and other serum proteins including immunoglobulins in synovial fluid and serum samples from 25 patients with ARF.

METHODS

Clinical material. 25 patients with joint effusion and ARF on the basis of the modified Jones criteria (1) underwent aspiration of the knee joint. They had been admitted to the San Fernando General Hospital in Trinidad and examined by one of us (M. S.) as part of our ongoing studies of streptococcal infections and their complications (8–10). 14 of the 25 patients were males; their ages ranged from 5 to 28 yr with an average of 14 yr. 16 patients (64%) had signs of carditis during this hospitalization. All of the patients responded favorably to treatment with salicylates.

25 age- and sex-matched subjects were selected from healthy inhabitants of a village in Trinidad which was representative of areas where many of the patients lived. Serum samples were obtained from these control subjects for comparison of serum proteins with those of the patients.

Collection of specimens. Synovial fluid and blood samples were obtained within minutes of each other soon after the patient's admission to the hospital. 10–15 ml of synovial fluid were aspirated from the knee joint through an 18-gauge needle into a plastic syringe. One portion of synovial fluid was examined for leukocytes by total and differential counts. The remainder was freed of cellular elements and clots, as were the serum samples, by centrifugation at 600 *g* for 20 min at room temperature. Both serum and synovial fluid samples were frozen immediately after their separation and stored at −20°C for several weeks and at −70°C thereafter until studied. When thawed, the synovial fluid samples were divided and approximately 1.5 U of hyaluronidase (Wydase, Wyeth Laboratories, Philadelphia, Pa.) was added to a 5-ml portion of each.

Assays of proteins. Total protein concentrations of both synovial fluid and serum samples were determined by the biuret method (11). Protein electrophoresis of serum and hyaluronidase-treated synovial fluid samples was performed on cellulose acetate membranes using a Beckman model R-100 microzone electrophoresis system (Beckman Instruments, Inc., Fullerton, Calif.). The electrophoretic curve was obtained with a Beckman R-110 microzone densitometer. Albumin concentration was calculated from the total protein and the percentage of albumin on the electrophoretic curve. Concentrations of IgG, IgM, IgA, transferrin, α_2-macroglobulin, C1q, C3, and C4 were determined by radial immunodiffusion (12, 13). Immunoplates for determinations of IgG, IgM, IgA, and C3 were prepared in our laboratory using appropriate dilutions of monospecific antisera and standards from Hyland Div., Travenol Laboratories, Inc. (Costa Mesa, Calif.) in 0.6% ion agar. C1q immunoplates and standards were kindly provided by Dr. Henry Gewurz (Rush Medical College, Chicago, Ill.). Immunoplates for

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[1] *Abbreviations used in this paper:* ARF, acute rheumatic fever; SF/S, ratio of synovial fluid to serum.

TABLE I

Serum Proteins in 25 Patients with ARF Compared with Normal Subjects and Related to Synovial Fluid Proteins in the Patients

Protein studied	Patients' serum values*	Control subjects' serum values*	Patients' synovial fluid values*	Patients' SF/S values*
Total, g/100 ml	7.49§±0.68	8.60±0.60	4.27±0.86	0.57±0.21
Albumin, g/100 ml	2.81§±0.42	4.50±0.23	1.91±0.38	0.69±0.13
Globulin, g/100 ml	4.68‡	4.10‡	2.36‡	0.68
Albumin/globulin	0.60§±0.10	1.12±0.14	0.84±0.19	0.81±0.12

* Values in terms of mean±SD.

‡ Obtained by subtracting mean albumin from mean total protein values.

§ Decreased from control value ($P < 0.01$ or less).

determinations of C4 were obtained from Meloy Laboratories Inc., (Springfield, Va.) whereas those for α_2-macroglobulin and transferrin were obtained from Hyland laboratories. Although no significant differences were noted in size of the precipitation rings when representative paired samples of hyaluronidase-treated and untreated synovial fluids were studied, all presently reported concentrations of protein in synovial fluids were derived from the samples treated with hyaluronidase as advocated by others (14).

Calculations. Ratios of the concentration of each protein in the synovial fluid to its concentration in serum were obtained for each patient. These ratios are referred to as SF/S values. Correlation coefficients were calculated by Pearson's formula (15) for: serum and synovial fluid concentrations of respective proteins; synovial fluid concentrations of single proteins and the total protein content of respective synovial fluids; synovial fluid concentrations of paired proteins; and SF/S values of paired proteins. Correlation coefficients also were obtained for the SF/S values of each protein and the total protein content of respective synovial fluids and regression lines were obtained by the least squares method (15). Finally, the log of the mean SF/S value for each protein was plotted against the log of the respective protein's molecular weight according to Kushner and Somerville (14). A regression line was obtained for the nonimmunological proteins (albumin, transferrin, and α_2-macroglobulin) and the IgG and IgM globulins. The expected mean SF/S values for the remaining proteins (complement components and IgA globulin) were derived from this regression line by the formula: $\log Y = a + (b)(\log X)$, where Y is the expected mean SF/S value of the protein, "a" is the intercept of the regression line in the ordinate, "b" is the regression coefficient or slope of the line and X is the molecular weight of the protein. The probability of the difference between expected and obtained values was computed by the two-sided t test (15). Computations were performed with a Programma 101 computer (Olivetti, Underwood Corp., New York).

TABLE II

Serum Immunoglobulins and Complement Components in 25 Patients with ARF Compared with Normal Subjects and Related to Synovial Fluid Proteins in the Patients

Protein studied	Patients' serum values*	Control subjects' serum values*	Patients' synovial fluid values*	Patients' SF/S values*
	mg/100 ml	*mg/100 ml*	*mg/100 ml*	
IgG	1,632‡±447	1,457±355	990±355	0.62±0.20
IgM	203‡±115	110±43	91±53	0.47±0.17
IgA	394‡±121	283±128	210±119	0.50±0.16
C1q	23‡±8	15±3	10±6	0.43±0.21
C3	180‡±31	128±19	103±25	0.56±0.11
C4	45‡±17	32±8	20±10	0.46±0.16
α_2-Macroglobulin	286±56	275±90	147±50	0.52±0.17
Transferrin	247±75	270±65	174±57	0.73±0.21

* Values in terms of mean±SD.

‡ Increased over control value ($P < 0.01$).

RESULTS

Most patients experienced prompt relief of local pain after joint fluid aspiration. Neither pain nor swelling recurred in any case.

Leukocytosis was present in the synovial fluids with an average of 29,000 leukocytes/mm^3 (range 2,000–96,000 leukocytes/mm^3). Only five samples contained less than 10,000 leukocytes/mm^3. Polymorphonuclear leukocytes made up 83% of the leukocytes (average), ranging from 56 to 95%. No bacteria were observed on direct smear or in cultures of the synovial fluid samples.

Total serum proteins of the patients were in the range generally considered to be normal with a mean value of 7.49 g/100 ml while they were increased in many control subjects with a mean value of 8.6 g/100 ml (Table I). Serum albumin was decreased in the patients with ARF ($P < 0.01$) when compared with the control subjects who had concentrations generally considered to be normal. In contrast, serum globulins were increased in both patients and control subjects and were responsible for the increased total serum proteins in the control group.

The average serum concentrations of each immunoglobulin and of C1q and C3 were significantly increased in patients when compared with the control subjects (Table II). Serum C4 also appeared to be increased in patients with ARF but this increase was not significant ($P > 0.1$). Serum α_2-macroglobulin and transferrin val-

TABLE III

Correlations between the SF/S Values of Respective Immunoglobulins and Complement Components

Protein	Correlation with				
	IgM	IgA	C1q	C3	C4
IgG	$r = 0.476$ $P < 0.02$	$r = 0.407$ $P < 0.05$	$r = 0.116$ $P > 0.50$	$r = 0.302$ $P > 0.10$	$r = 0.015$ $P > 0.90$
IgM		$r = 0.507$ $P < 0.01$	$r = 0.396$ $P < 0.05$	$r = 0.498$ $P < 0.02$	$r = 0.242$ $P > 0.20$
IgA			$r = 0.648$ $P < 0.01$	$r = 0.513$ $P < 0.01$	$r = 0.605$ $P < 0.01$
C1q				$r = 0.267$ $P > 0.10$	$r = 0.411$ $P < 0.05$
C3					$r = 0.593$ $P < 0.01$

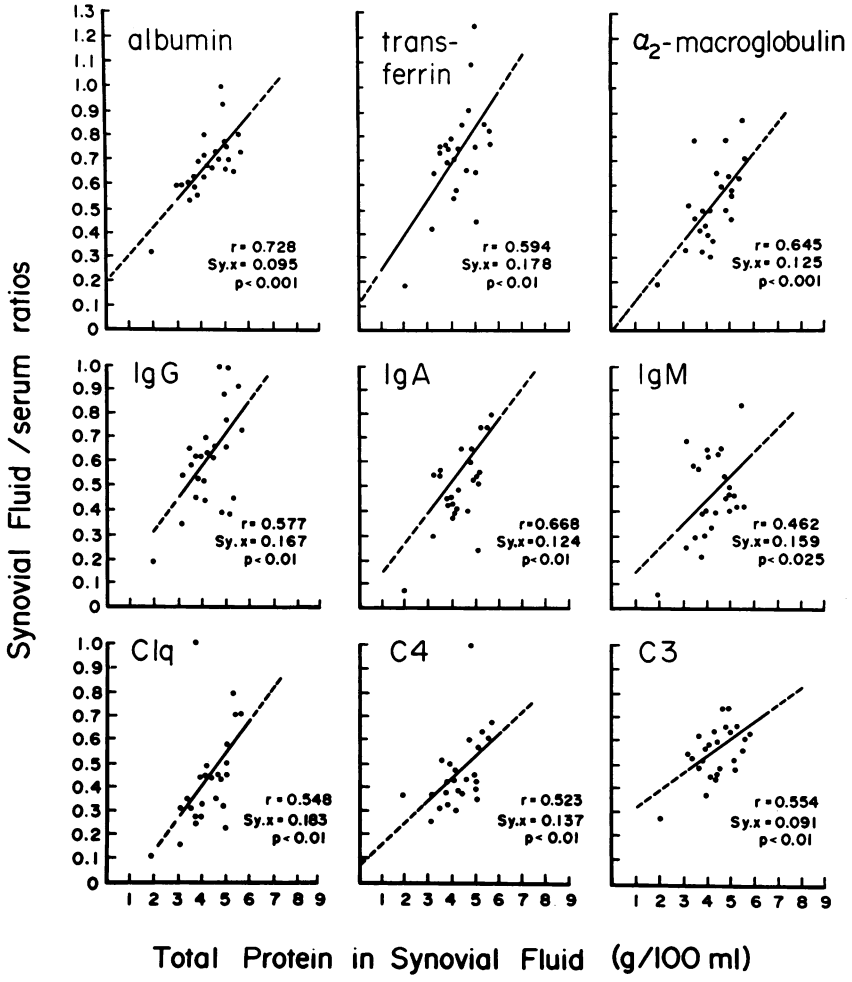

FIGURE 1 Ratios of SF/S values of the proteins studied to the concentration of total protein in respective synovial fluids. r = correlation coefficients. Sy.x = standard error of the values from the line.

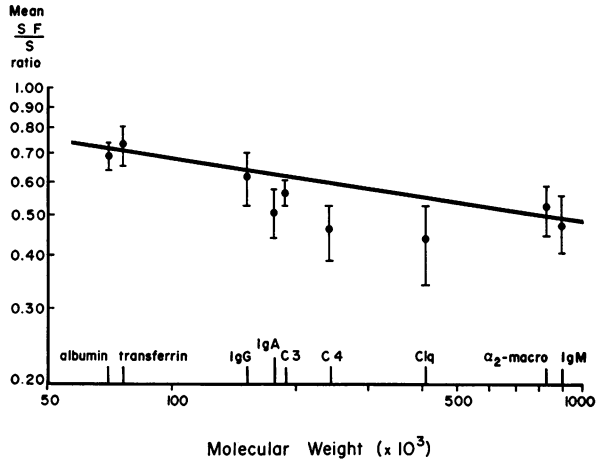

FIGURE 2 Correlation between the ratios of the SF/S values of the proteins studied and their respective molecular weights. The heavy line represents the regression curve obtained from the SF/S values for albumin, transferrin, and IgG, α_2-macroglobulin and IgM globulins. Each black circle represents the mean of 25 values. The vertical bars represent the SDs of the 25 values.

ues did not differ significantly in the patients and the control subjects ($P > 0.1$).

No significant correlation was found between the serum and synovial fluid concentrations of any single protein nor between the synovial fluid concentrations of any single protein and the total protein content of respective synovial fluids. Significant correlation was found between the synovial fluid concentrations of C1q and C4 ($P < 0.02$) but not between any of the other proteins assayed. When correlation coefficients were determined for all possible paired combinations of the proteins by plotting the SF/S value for each protein against the SF/S value for each of the other proteins in each of the 25 respective patients, significant correlations were found among all three immunoglobulins (Table III). IgG did not correlate with any of the complement proteins while IgM correlated with C1q and C3 but not with C4. IgA correlated with all of the three complement proteins. C1q correlated with C4 but not C3. Nonetheless, C4 correlated with C3. The SF/S values for each protein correlated significantly with the total protein concentrations of the respective synovial fluids as shown in Fig. 1.

A highly significant linear correlation existed between the logs of the mean SF/S values for albumin, transfer-

TABLE IV

Comparison of the Mean SF/S Values Obtained for IgA, C1q, C4, and C3 with Those Expected from Their Respective Regression Lines

Protein	SF/S value obtained	SF/S value expected	*P* value
IgA	0.505	0.621	<0.005
C1q	0.434	0.548	<0.02
C4	0.459	0.591	<0.001
C3	0.561	0.614	<0.02

SF/S value = synovial fluid/serum value for respective proteins.

TABLE V

Relationships of Serum and Synovial Fluid Proteins to Each Other, to Total Protein in Synovial Fluids, and to Respective Molecular Weights

First factor	Second factor	Positive correlation
Serum value of each protein	Synovial fluid value of respective protein	No
Synovial fluid value of each protein	Total protein in respective synovial fluid	No
Synovial fluid value of each protein	Synovial fluid value of each other protein	C1q, C4 only
SF/S value of each protein	SF/S value of each other protein	Partial*
SF/S value of each protein	Total protein in respective synovial fluid	Yes‡
Log SF/S value of each protein	Log of respective protein's mol wt, Stokes radius, and friction coefficient	Yes§

* See Table III.
‡ See Fig. 1.
§ See Fig. 2.

rin, α_2-macroglobulin, IgG, and IgM and the logs of their respective molecular weights ($P < 0.005$) as shown in Fig. 2. The calculated correlation coefficient was $r = 0.980$. The standard error for these five points based on a regression line best fitted to them was only 0.018 which indicates that the values for these proteins fell very close to a straight line. The logs of the mean SF/S values for IgA, C1q, C3, and C4 fell below this regression line. These deviations from the straight line were significant when expected values were compared to observed values in Table IV. When the logs of the mean SF/S values for all proteins were plotted against the logs of their respective Stokes radii or their respective friction coefficients, the results were similar to those shown in Fig. 2.

All of the correlations are summarized in Table V.

DISCUSSION

The amount of a complement component in serum does not necessarily indicate the amount of its participation in a disease process (7) since serum levels depend on the synthesis and catabolism of complement as well as on its fixation or consumption (16). Even so, although serum complement levels in rheumatoid arthritis usually are above normal (17, 18), local consumption of complement has been reported within the joints in this disease (2–5). Local activation of complement also has been implicated within the central nervous system (19) and the pericardium (20) in patients with lupus erythematosus. Increased serum levels of both total complement and C3 also have been described in patients with ARF (21, 22). However, no analysis of complement within the joints or other likely sites for its local consumption has been reported in ARF patients. This lack of information led us to examine the synovial fluid of patients with ARF for immunological clues to the pathogenesis of this arthritis.

The concentration of a serum protein in synovial fluid depends upon its concentration in the serum and the degree of synovial permeability present (23, 24) except when local synthesis or destruction occurs. Hedberg (4) showed a high correlation between complement and total protein in synovial fluids of patients with degenerative joint disease when these values were corrected for serum levels by employing the SF/S values. Likewise, the concentrations of proteins assayed in the synovial fluids of our patients with ARF correlated significantly with the total protein concentrations of the synovial fluids when corrected for their serum concentrations by employing the SF/S values. Furthermore, Kushner and Somerville (14) found that although the correlation between the mean SF/S values of nonimmune proteins and their respective molecular weights was linear in four different types of rheumatic diseases (classical rheumatoid arthritis with positive rheumatoid factor, probable rheumatoid arthritis with negative rheumatoid factor, gouty arthritis, and osteoarthritis), the slopes of the lines, which indicate the relative permeability to proteins according to molecular weights, were markedly different for each type of arthritis. Thus, the permeability of the synovium to proteins appears to depend not only on the molecular weight of the proteins and their concentration in the serum but also on the type of disease process involved. Concentrations of whole complement and complement components also were found to vary in synovial fluids from patients with different kinds of rheumatic diseases even when corrected for serum levels and synovial permeability (2). The clinical homogeneity of the patients examined in the present study allowed us to assess the relation of complement components to each other and to immunoglobulins and other plasma proteins in a single pathogenetic type of disease.

Since the SF/S value of a protein reflects the permeability of the synovium, changes in the SF/S values of all proteins from one patient should be in the same direction if proteins are not being locally produced or destroyed. In the studies by Kushner and Somerville (14) SF/S values indicated local production of IgG and IgM in patients with classical rheumatoid arthritis. In the present study, there was no evidence for local synthesis of IgG or IgM since their mean SF/S values fell in line with the nonimmunological proteins. However, there was evidence for local consumption of the complement components. Despite the generally increased serum levels of C1q, C3, and C4 which may represent acute phase reactants (22) in our patients, these proteins were relatively decreased in synovial fluid so that the SF/S values fell below the regression line formed by the other serum proteins except for IgA. In these calculations, C1q was considered to have a mol wt of 400,000 (25). Inasmuch as C1q is likely to be complexed with C1r and C1s in serum and synovial fluid, use of a larger mol wt might be more realistic. While the actual mol wt of the C1 complex has not been established, addition of those of the separate components results in a mol wt of around 700,000. Thus, the SF/S value for C1q (as C1qrs) may belong farther down the regression line. Although still well below the line at 700,000, the difference becomes of less significance ($P < 0.1$).

The apparent correlation of IgA with the complement components probably does not represent immunological activity as IgA does not fix complement by the classic pathway (26) and thus should not decrease C1q and C4. The decreased amounts of IgA in the synovial fluids may reflect instead its presence in the serum as polymers which would result in impaired passage of the larger molecules through the synovium as well as un-

derestimation of the molecular weight of IgA in Fig. 2. In addition, the use of monomer IgA for standards in our assays would give falsely low values were polymers present in serum or synovial fluids or were secretory IgA present in synovial fluid (27).

Thus, the methods employed as used in this study indicate independently decreased synovial fluid values for C1, C4, and C3 which may be considered further evidence for activation of complement within the joints and the only evidence to date for this occurrence in ARF. Such local activation of C3 with consequent formation of chemotactic and vasoactive fragments (28) may account for the presence of many leukocytes in these synovial fluids in the absence of bacteria as well as the presence of the fluid itself. A possible role for the alternate pathway to complement should be considered in this activation as chemotactic and vasoactive factors may be released through the alternate as well as the classic pathway. In our observations, however, the earlier components were more depressed than C3 which suggests a major role for the classic rather than the alternate pathway although both may be involved. Both C1 and C3 also may be activated directly by plasmin (28). A relationship of this activity to our observations is a distinct possibility as both fibrinogen and evidence of fibrinolysis have been observed within joint fluids in other rheumatic diseases (29). These factors were not examined in the present study. However, C3 is more susceptible to plasmin than C1q and in turn, C4 (28), while C1q and C4 were more depressed than C3 in the present study.

Our data, therefore, suggest that activation of complement occurs through the classic pathway within the joints of patients with ARF. If such activation were by immune complexes formed within the joint fluid, IgG or IgM should be correspondingly decreased within the fluid (unless locally increased production of immunoglobulins exactly balanced their depletion which seems unlikely), while if it were by circulating immune complexes, serum values of complement should be decreased as well as the synovial fluid values. Neither of these conditions was observed. Immune complexes formed or trapped in the synovial membranes, however, might well fix and activate complement components as they pass through, thus depleting the synovial fluid of complement and playing a major role in the local inflammation suffered by these patients with ARF. Our data favor this hypothesis.

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