

Reticuloendothelial Fc receptor function in patients with Sjogren's syndrome

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SUMMARY

The functional status of the reticuloendothelial Fc receptor in patients with Sjogren's Syndrome was examined by determining the clearance from the circulation of IgG coated erythrocytes which had been obtained from a single donor. 18 patients with Sjogren's Syndrome were studied and the results compared with those obtained from 18 patients with Rheumatoid Arthritis and 27 healthy controls. Abnormal Fc mediated clearance was observed in 3 individuals with Sjogren's Syndrome and 2 patients with Rheumatoid Arthritis. Extraglandular disease was not associated with abnormal Fc function and there was no correlation between the clearance rates and the immune complex levels, complement levels or rheumatoid factor titre. A comparison of the clearance rates obtained using the patients own red cells with those derived from using a single donor showed that the source of cells used had a significant effect on the clearance rate. Our findings provide no support for the idea that defective Fc function may be of pathogenic significance in the development of more extensive disease in patients with Sjogren's Syndrome.

Keywords reticuloendothelial system Fc receptor Sjogren's syndrome

INTRODUCTION

Whenever IgG coated autologous erythrocytes have been used to measure reticuloendothelial system Fc function in man it has been assumed that differences in the clearance rates of these cells reflect differences in the function of the macrophage Fc receptor. As a result of these studies it is now widely believed that Fc abnormalities are common in patients with a variety of connective tissue diseases and that they contribute to the pathogenesis of the disease by impairing the removal of immune complexes from the circulation (Frank, *et al.*, 1979; Lockwood *et al.*, 1979; & Kimberley *et al.*, 1983).

In a recent study we have shown that the clearance rate of IgG coated erythrocytes is also influenced by the property of the infused cell (Williams, O'Sullivan & Ratanachaiyauong, 1985). Since most of the comparative studies of Fc function have failed to eliminate this variable from their studies we felt it appropriate to re-examine the hypothesis that Fc abnormalities occur in patients with immune complex mediated diseases. We chose to study patients with Sjogren's Syndrome, a disorder in which Fc abnormalities are believed to regulate the clinical expression of this disease (Hamburger *et al.*, 1979).

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MATERIALS AND METHODS

Patient selection. Thirty-six patients, six men and thirty women, currently attending either the Department of Rheumatology or the Department of Oral Medicine, University Hospital of Wales were studied. All patients had a rhesus positive blood group and fulfilled the criteria for the diagnosis of Sjogren's Syndrome (Moustophoulos *et al.*, 1979), SLE (Tan *et al.*, 1982) and either classical or definite rheumatoid Arthritis (Ropes *et al.*, 1958). Patients were divided into three categories. Seven patients had disease confined to the exocrine glands, eleven patients had either involvement of extraglandular tissue or an associated connective tissue disease and eighteen patients had either classical or definite Rheumatoid Arthritis (Table 1).

The control subjects were healthy volunteers, they were not taking any medication, did not have a history of jaundice and none had received any blood transfusion. The donor for the red cell suspension was healthy, had never been jaundiced, was negative for hepatitis B antigen and had the blood group O Rhesus positive, Kell negative. Compatibility between the donor cell suspension and the recipients was tested by the Blood Bank at the University Hospital of Wales, Cardiff.

Informed consent was obtained from all subjects and Ethical Committee Approval was granted by the Division of Medicine, University Hospital of Wales.

Clearance studies of the antibody coated red blood cells (IgG RBC). The preparation of the antiserum, labelling of the red cells and their subsequent coating with antibody was carried out as previously described (Williams *et al.*, 1985).

Immune complex studies. Immune complexes were detected by the Clq binding assay (Zubler *et al.*, 1976) and by the monoclonal rheumatoid factor binding assay (Barratt & Naish, 1979).

Complement levels and rheumatoid factor activity. Quantitation of C3 and C4 levels was carried out by radial immunodiffusion using commercial antisera. Rheumatoid factor activity was detected using latex agglutination and quantified using the sheep cell agglutination test.

RESULTS

The clearance times of IgG coated erythrocytes which had been obtained from a single donor varied between 20 min and 81 min in the normal population (Fig. 1). The upper 95% confidence limit for this group was 71 min. Abnormal clearance times were only seen in five out of the 37 patients studied and in four of these the increase in the $T_{1/2}$ was a modest one. Only one patient had a substantially prolonged clearance of the IgG coated erythrocytes.

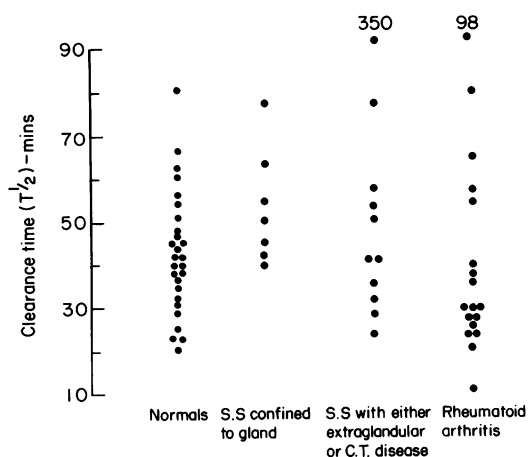


Fig. 1. Clearance times of the IgG coated erythrocytes in control subjects and patients with Sjogren's Syndrome and Rheumatoid Arthritis.

Table 1

Patient	Sex	Age	Nature and Extent of Disease	Lip biopsy	Drug Treatment
1	F	44	Limited to exocrine glands	+	Nil
2	F	64	Limited to exocrine glands	+	Nil
3	F	50	Limited to exocrine glands	+	Nil
4	F	61	Limited to exocrine glands	+	Nil
5	F	42	Limited to exocrine glands	+	Nil
6	F	46	Limited to exocrine glands	+	5 mg Prednisone/day
7	M	48	Limited to exocrine glands	+	Nil
8	F	73	Rheumatoid Arthritis	+	Nil
9	F	76	Rheumatoid Arthritis & Histiocytic lymphoma	+	Prednisone 7.5 mg/day
10	F	50	Rheumatoid Arthritis	+	Prednisone 5 mg/day
11	F	45	S.L.E.	+	Nil
12	F	59	S.L.E.	+	Azathioprine 50 mg, Prednisone 5 mg
13	F	60	Scleroderma	+	Nil
14	F	43	Raynaud's Phenomenon. Vasculitic leg ulcers	+	Nil
15	F	72	Rheumatoid Arthritis	+	Prednisone
16	F	52	Rheumatoid Arthritis	+	Nil
17	F	59	Interstitial pneumonitis	+	Azathioprine 50 mg/day
18	F	54	Raynaud's phenomenon, calcinosis, interstitial pneumonitis.	+	Nil

Patients 19-36, 18 patients with Rheumatoid Arthritis and normal tear production as measured by a Schirmer test, (5 male, 13 female. Age range 34-72). Eleven treated with either Gold or Penicillamine and one other receiving 5 mg Prednisone/day.

In Fig. 2 we show that the clearance time for the IgG coated cells in both normal controls and patients with Sjogren's Syndrome is influenced by the source of red cells used. In the control group, three individuals who were identified as having a prolonged $T_{1/2}$, and by inference abnormal Fc function, reverted to normal when a different red cell suspension was used. A similar phenomenon was observed in the patients with Sjogren's Syndrome. We were only able to identify one patient in whom the red cell clearance study revealed delayed clearance with both the autologous and donor cells.

Immune complexes, determined by the Clq binding assay and the monoclonal rheumatoid factor binding assay were detected in the sera of patients with Sjogren's syndrome and rheumatoid Arthritis (Fig. 3 & Fig. 4). The frequency of immune complexes was similar in all three groups studied. No correlation was observed between the immune complex levels, determined by either assay, and the red cell clearance time (Data not shown).

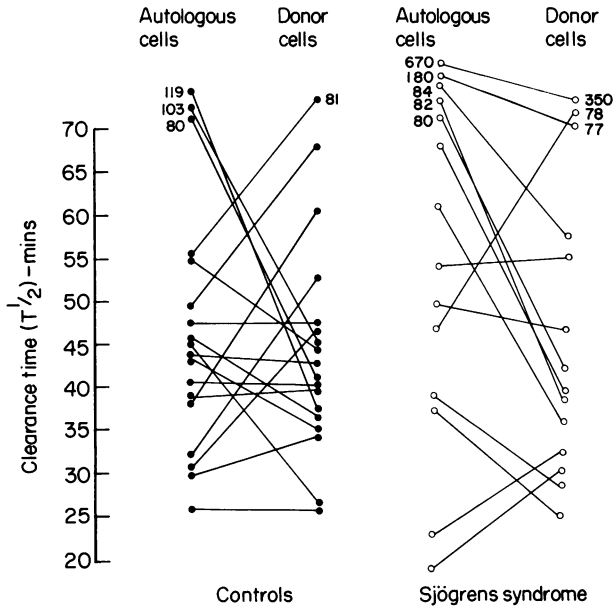


Fig. 2. Comparison of the clearance times obtained with autologous red cells and red cells obtained from a single donor.

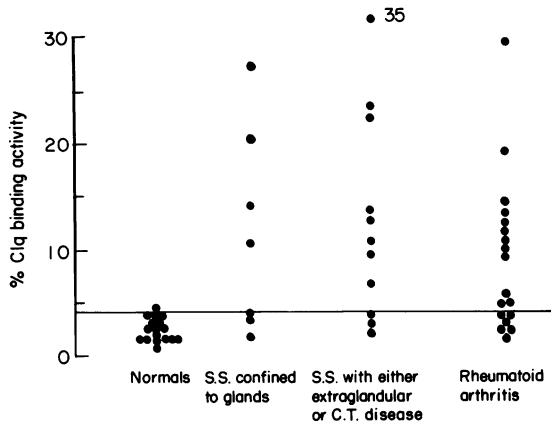


Fig. 3. Immune complex levels determined by Clq binding assay in normal individuals and patients with Sjogren's syndrome and Rheumatoid Arthritis. Horizontal line represents upper 95% confidence limit in the control population.

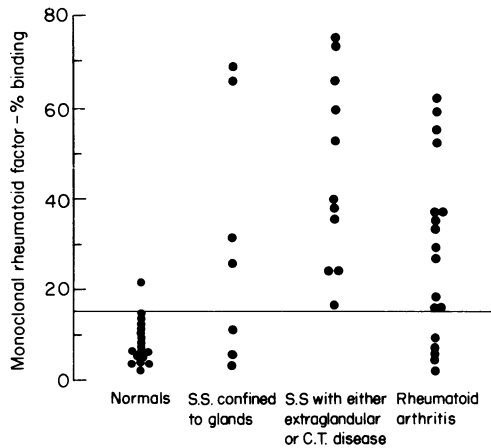


Fig. 4. Immune complex levels determined by rheumatoid factor binding assay in patients with Sjogren's Syndrome and Rheumatoid Arthritis. Horizontal line represents upper 95% confidence limit in the control population.

Serum C3 and C4 levels were measured in all patients, Three patients had low levels of both proteins, one had localized disease, one had Sjogren's Syndrome in association with SLE and the third patient had rheumatoid vasculitis. We did not find any correlation between the presence or absence of rheumatoid factor and a slow red cell clearance.

DISCUSSION

The most important finding to emerge from this study is that when IgG coated red cells are obtained from a single source putative associations between Fc function and disease features in patients with Sjogren's Syndrome are no longer demonstrable. We were unable to show any significant difference in the Fc function of a normal control population and patients with Sjogren's Syndrome or Rheumatoid Arthritis even though these two groups had abundant immune complexes present in the circulation. The reason for this discrepancy is not clear at the present time.

Since the property of the red cell can influence its clearance rate it follows that an accurate assessment of Fc function can only be achieved when this variable is eliminated. Our results show that it is possible for normal individuals to have prolonged clearance times, a finding which is not indicative of defective Fc function but is simply due to differences between their red cells and those of other individuals. Variations in the number of rhesus antigens expressed on the red cell surface of different individuals is presumably responsible for the different rates at which these cells are cleared *in vivo* (Rochna & Hughes, 1965).

Comparative studies of Fc function in disease are therefore misleading for two reasons. The property of the red cell influences the clearance rate independently of macrophage function and certain cell suspensions may be more readily inhibited by circulating immune complexes. In support of the second suggestion experiments which we have carried out in the rat, using erythrocytes coated with monoclonal antibodies, have shown that reducing the number of antigens on the red cell surface renders these cells much more susceptible to inhibition by immune complexes (unpublished observations). It is of interest to note that when a single source of red cells has been used to prepare IgG coated erythrocytes both the association between HLA antigen DR3 and abnormal Fc function in normal individuals and patients with Systemic Lupus Erythematosus are lost (Williams *et al.*, 1985 & Van der Woude *et al.*, 1984).

In conclusion this paper challenges the view that abnormalities in Fc function are common in patients with the connective tissue diseases and that Fc defects contribute to the extent of the clinical disease in patients with Sjogren's Syndrome.

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