Ann. rheum. Dis. (1970), **29**, 681

Serum immune globulins in Sjögren's syndrome

J. M. GUMPEL AND J. R. HOBBS

Departments of Medicine and Chemical Pathology, Royal Postgraduate Medical School, London

Sjögren's syndrome, a disease principally affecting exocrine glands but with systemic manifestations, is characterized by hypergammaglobulinaemia and the presence of a wide variety of autoantibodies. These are of several types, both organ and non-organ specific, complement-fixing, and precipitating antibodies, and in general are found in a higher proportion of patients than, for instance, in systemic lupus erythematosus (SLE). Unlike SLE, however, circulating immune complexes with DNA are not found. As autoantibodies are immunoglobulins, it is surprising that no survey of immunoglobulin levels in Sjögren's syndrome is available other than in a few patients, although a considerable amount of similar information exists for rheumatoid arthritis and SLE.

As part of a study of patients with Sjögren's syndrome, levels of IgG, IgA, and IgM were determined.

Material and methods

Patients were considered to have Sjögren's syndrome if they had two or more features of the diagnostic triad: keratoconjunctivitis sicca; xerostomia and/or salivary gland enlargement; rheumatoid arthritis or another connective tissue disorder. None had sarcoidosis or malignant lymphoma. All had keratoconjunctivitis sicca, and because of this were attending a special clinic at Moorfields Eye Hospital, City Road, London.

For comparison, immunoglobulin levels were estimated in 23 patients with rheumatoid arthritis without sicca components attending a clinic at the Hammersmith Hospital, who had been selected to give a reasonable age and sex match, and to approximate to the duration of disease of the patients with Sjögren's syndrome with rheumatoid arthritis.

Serum immunoglobulin levels were determined by a modification of the Mancini Technique (Hobbs, 1970a). The standards used for calculation are the geometric means based on 107 adults (54 males; 53 females).

The geometric means and normal (± 2 S.D.) range in mg./100 ml. are as follows (see also Figure):

Mean	*Range*
IgG 947	500-1600 (48-168 per cent.)
IgA 248	125-425 (50-172 per cent.)
IgM 94	47-170 (50-180 per cent.)

53 females only:

IgG 986	540-1800 (104 per cent.; 57-190 per cent.)
IgA 242	128-460 (98 per cent.; 51-186 per cent.)
IgM 106	54-207 (113 per cent.; 58-220 per cent.)

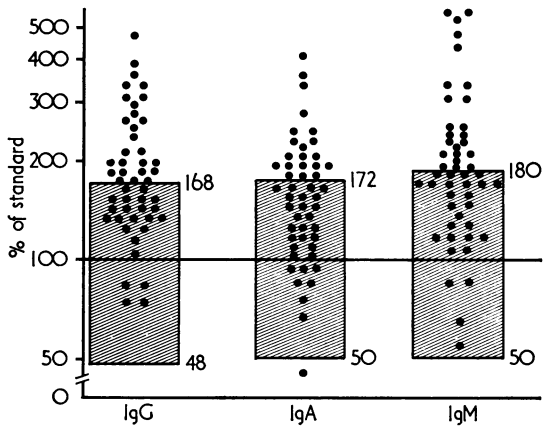

FIGURE *Distribution of serum levels of IgG, IgA, and IgM in fifty patients with Sjögren's syndrome. Normal ranges are shown hatched.*

Results

Considerable elevation of serum levels of all three immunoglobulin classes was found in the fifty patients with Sjögren's syndrome, and the geometric means of IgG and IgM were elevated above the 95 per cent. level for the normal population (Table I). As the study group consisted of 44 females and six males, some allowance must be shown for the higher levels found in women, but the increase in levels is still marked.

Table I *Immunoglobulin levels in fifty cases of Sjögren's syndrome (expressed as percentage of geometric mean of 107 normals)*

Immunoglobulin	*Geometric mean*	*Range (± 2 S.D.)*
G	174	77 to 394
A	149	64 to 349
M	183	67 to 502

Simultaneous elevation of all three immunoglobulins was found in seven patients, and of two immunoglobulins in a further sixteen (Table II). Serum electrophoresis did not show any monoclonal bands. One patient was found to have IgA

of a normal level but with the dense precipitin ring Hobbs (unpublished) finds in Waldenström's hyperglobulinaemic purpura. This patient's IgG level was 475 per cent. of standard, and IgM 202 per cent. of standard. She in fact had hyperglobulinaemic purpura together with the sicca syndrome and pulmonary fibrosis, and on sternal marrow examination increased numbers of plasma cells of normal morphology were found. No Bence-Jones protein was found (Gumpel, In press).

On considering the immunoglobulin levels in the individual groups (Table III), *i.e.* in those with the sicca syndrome alone, those with systemic sclerosis, and those with rheumatoid arthritis—little difference can be found between the group with sicca syndrome alone and the group with rheumatoid arthritis. IgA levels were slightly higher in the patients with Sjögren's syndrome with rheumatoid arthritis than in those with the sicca syndrome only. All three immunoglobulin levels were more elevated in the patients with Sjögren's syndrome than in those with uncomplicated rheumatoid arthritis.

The four patients with systemic sclerosis surprisingly had higher levels of IgG and IgM than the other groups.

Little correlation was found between elevated serum immunoglobulin levels and factors such as duration of disease, age, presence or absence of rheumatoid or antinuclear factors, except amongst the patients with rheumatoid arthritis and sicca features. Here, those with an elevated IgM level tended to have a longer period of disease (19.2 *v.* 12·7 years) and a higher titre of rheumatoid factor. Immunoglobulin levels were unlikely to have been affected by treatment, as only a few patients with Sjögren's syndrome and rheumatoid arthritis had received gold or were on moderate doses of steroids, and only two patients with the sicca syndrome were taking moderate or minute doses of steroids.

Discussion

The known predisposition of patients with Sjögren's syndrome to immunological hyper-responsiveness

Table II *Patterns of immunoglobulin elevation in individual patients*

Immunoglobulin			*Cases of Sjögren's syndrome*			
G	*A*	*M*	*All*	*Sicca syndrome only*	*With progressive systemic sclerosis*	*With rheumatoid arthritis*
+	+	+	7	3	1	3
+	−	+	5	2	2	1
+	+	−	7	3		4
−	+	+	4	2		2
+	−	−	6	3		3
−	+	−	3	2		1
−	−	+	3			3
None elevated			15	8	1	6
Total			50	23	4	23

+ elevated level

Table III *Immunoglobulin levels in fifty cases of Sjögren's syndrome grouped according to other diseases, and compared with 23 patients with rheumatoid arthritis alone*

Diagnosis		*Sjögren's syndrome*						*Rheumatoid arthritis*	
		Sicca components only (23)		*With progressive systemic sclerosis* (4)		*With rheumatoid arthritis* (23)		*Without sicca components* (23)	
		Mean age (yrs) 52	*Male: Female* 2 : 22	*Mean age (yrs)* 53	*Male: Female* 1 : 3	*Mean age (yrs)* 56	*Male: Female* 3 : 20	*Mean age (yrs)* 57	*Male: Female* 4 : 19
Immunoglobulin		Geometric mean	± 2 S.D.	Geometric mean	± 2 S.D.	Geometric mean	± 2 S.D.	Geometric mean	± S 2.D.
	G	177	69 to 450	210	117 to 378	168	83 to 337	126	30 to 530
	A	144	50 to 410	132	73 to 236	157	80 to 311	112	45 to 277
	M	171	66 to 445	303	82 to 1,120	181	69 to 474	127	38 to 432

would make an increase in immunoglobulin levels predictable, especially of IgG. Considerable elevation of IgG levels in SLE has been previously reported (Cass, Mongan, Jacox, and Vaughan, 1968), with little elevation of IgA or IgM. Compared with SLE, Sjögren's syndrome is a chronic and relatively benign disease. In autoimmune diseases with initially raised IgG, Hobbs (1970b) has observed subsequent elevation of IgM.

Some authors (Claman and Merrill, 1966; Barden, Mullinax, and Waller, 1967; Marcolongo, Carcassi, Frullini, Bianco, and Bravi, 1967) have found that the principal immunoglobulin abnormality in rheumatoid arthritis is an elevation of IgA. This was not confirmed by other workers (Veys and Claessens, 1968) nor was it reflected in the matched patients with uncomplicated rheumatoid arthritis in this study, although it has been found in random patients with rheumatoid arthritis at this hospital. The findings regarding IgG and IgM elevation have been variable. In this study there was a marked similarity of the elevated immunoglobulin levels in the patients with the sicca syndrome only and in those with Sjögren's syndrome with rheumatoid arthritis, although more frequent elevation of IgM was found in the latter, especially in comparison to the patients with uncomplicated rheumatoid arthritis. Bloch, Buchanan, Wohl, and Bunim (1965), who studied 62 patients with Sjögren's syndrome, had found more marked hypergammaglobulinaemia in cases of the sicca syndrome than in those with rheumatoid arthritis. In our four patients with systemic sclerosis, there was a very marked elevation of IgG and IgM, which was surprising, as immunoglobulins are not commonly elevated in systemic sclerosis. The four patients were also unusual in that three had telangiectasia, Raynaud's phenomenon, and acrosclerosis as their predominant lesion, and one had facial hemiatrophy and *coup de sabre* (Gumpel, Wright, and Holborow).

Heremans (1960) estimated immunoglobulin levels in four patients with Sjögren's syndrome, but in three of them diseases such as chronic active hepatitis were also present, and in the one relatively uncomplicated case the IgA and IgM levels were normal, but the IgG was not available. Some information on the immunoglobulin levels of the group of patients with Sjögren's syndrome studied at the National Institutes of Health can be gathered from the levels given for certain patients (Talal, Sokoloff, and Barth 1967; Talal, Zisman, and Schur, 1968; Talal, Asofsky, and Lightbody, 1970), and if one excludes the patients with reticulum cell sarcoma pseudolymphoma, and macroglobulinaemia, a general but moderate increase in IgG is found, with relatively normal levels of IgA and IgM.

Summary

Marked elevation of IgG and IgM levels were found in fifty patients with Sjögren's syndrome, and a lesser increase in IgA levels. There was little difference between patients with sicca components alone and those with rheumatoid arthritis, but in a smaller group with systemic sclerosis levels of all three immunoglobulins were very elevated. By comparison immunoglobulin levels were only modestly raised in patients with uncomplicated rheumatoid arthritis.

We wish to acknowledge the kindness of Prof. Barrie Jones and Mr. Peter Wright in allowing us to study their patients. We thank Mrs. Urmila Patel and Miss Janet Perks for their able technical assistance. J. M. Gumpel was supported by a grant from the Arthritis and Rheumatism Council.

References

BARDEN, J., MULLINAX, F., AND WALLER, M. (1967) *Arthr. and Rheum.*, **10,** 288 (Immunoglobulin levels in rheumatoid arthritis).

BLOCH, K. J., BUCHANAN, W. W., WOHL, M. J., AND BUNIM, J. J. (1965) *Medicine (Baltimore)*, **44,** 187 (Sjögren's syndrome).

CASS, R. M., MONGAN, E. S., JACOX, R. F., AND VAUGHAN, J. H. (1968) *Ann. intern. Med.*, **69,** 749 (Immunoglobulins G, A, and M in systemic lupus erythematosus).

CLAMAN, H. N., AND MERRILL, D. (1966) *J. Lab. clin. Med.*, **67,** 850 (Serum immunoglobulins in rheumatoid arthritis).

GUMPEL, J. M. *Proc. roy. Soc. Med.* (In press).

——, WRIGHT, P., AND HOLBOROW, E. J. In preparation.

HEREMANS, J. (1960) 'Les globulines sériques du système gamma', p. 286. Editions Arscia, Bruxelles.

HOBBS, J. R. (1970a) Ass. clin. Path. Broadsheet no. 68, May, 1970, 'Simplified radial immunodiffusion'.

—— (1970b) *Brit. J. Hosp. Med.*, **3,** 669 (Immune globulins in some diseases).

MARCOLONGO, R., CARCASSI, A., FRULLINI, F., BIANCO, G., AND BRAVI, A. (1967) *Ann. rheum. Dis.*, **26,** 412 (Levels of serum immunoglobulins in patients with rheumatoid arthritis).

TALAL, N., ASOFSKY, R., AND LIGHTBODY, P. (1970) *J. clin. Invest.*, **49,** 49. (Immunoglobulin synthesis by salivary gland lymphoid cells in Sjögren's syndrome).

——, SOKOLOFF, L., AND BARTH, W. F. (1967) *Amer. J. Med.*, **43,** 50. (Extrasalivary lymphoid abnormalities in Sjögren's syndrome.)

——, ZISMAN, E., AND SCHUR, P. H. (1968) *Arthr. and Rheum.*, **11,** 774 (Renal tubular acidosis, glomerulonephritis and immunologic factors in Sjögren's syndrome).

VEYS, E. M., AND CLAESSENS, H. E. (1968) *Ann. rheum. Dis.*, **27,** 431 (Serum levels of IgG, IgM, and IgA in rheumatoid arthritis).