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An IgG subclass imbalance in connective tissue disease

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SUMMARY A group of 16 patients with a disproportionate polyclonal increase in their serum IgG1, resulting in raised concentrations of total IgG immunoglobulin, has been discovered. The other IgG subclasses in these patients are either normal or slightly reduced, resulting in an IgG1:IgG2 ratio of at least 10:1. Most cases are marked by the presence of anti-extractable nuclear antigen (anti-ENA) antibodies and high titres of rheumatoid factor and antinuclear antibody. All but one patient has a connective tissue disease, nearly twice the prevalence found in similarly hypergammaglobulinaemic patients without this IgG subclass imbalance. Among patients with systemic lupus erythematosus (SLE), those with the IgG1 disorder have a higher prevalence of high titre rheumatoid factor and antinuclear antibody, but a lower prevalence of anti-double-stranded DNA (anti-dsDNA) antibodies above 30 U/ml. It is suggested that this immunoglobulin abnormality may reflect a unique immunoregulatory dysfunction in these patients.

Key words: antinuclear antibody, autoantibody, immunoregulation, immunoglobulin, systemic lupus erythematosus.

Immunoglobulin abnormalities have been reported in association with connective tissue diseases (CTD). Systemic lupus erythematosus (SLE), for example, is characterised by hypergammaglobulinaemia, increased spontaneously activated B cells, and increased immunoglobulin-secreting cells in both patients and mouse models of the disease.[1–5] CTD are also characterised by autoantibody formation. These antibodies, such as antigammaglobulin, antinuclear, anti-RNP, anti-Sm, anti-La, and anti-DNA antibodies, are predominantly of the IgG1 and IgG3 isotypes.[6–10] This probably reflects the chemical nature of the antigenic determinant(s) against which these antibodies are directed, as protein antigens mostly induce an IgG1 antibody response with minor contributions from IgG3 and IgG4,[8 11] whereas carbohydrate antigens induce mainly IgG2.[8 11]

Although hypergammaglobulinaemia and IgG1 autoantibodies have been reported in CTD, this report highlights an imbalance in the IgG subclass concentrations in a small number of patients, mostly suffering from CTD. We consider the clinical implications of this new observation and discuss possible mechanisms for the immune dysregulation.

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Patients and methods

PATIENTS

Blood samples are referred to this regional immunology service laboratory from over 60 hospitals in the north west of England, and the tests performed are largely requested by the referring clinician. The patients who comprise this study represent the 600 examined for IgG subclass estimations between 1983 and 1986. Any bias in the sample relating to age, sex, or diagnosis, therefore, comes from the selection of this investigation by the referring clinician.

METHODS

Estimation of serum concentration of immunoglobulin and IgG subclass

Concentrations of IgG, IgA, and IgM immunoglobulins were measured by rate nephelometry

(Beckman RIIC Ltd, US). The amounts of IgG1, IgG2, and IgG3 were measured by radial immunodiffusion. Briefly, plates were poured with 1% agarose in barbitone buffer pH 8·0 containing 6% polyethylene glycol (mol. wt 3000) and dilutions of the monoclonal antibodies (MAbs; Unipath Ltd, Bedford, UK) against the IgG subclasses. The MAbs were diluted 1 in 90 for IgG1 (MAb clone JL512), 1 in 45 for IgG2 (MAb clone GoM1), and 1 in 180 for IgG3 (MAb clone ZG4). Samples of patients' serum (5 µl) were diluted 1 in 5 with phosphate buffered saline pH 7·6, placed in cut wells, and incubated for 72 hours at 4°C in a damp box. The precipitin ring diameters were compared with those obtained from a standard curve produced by doubling dilutions of the protein reference serum SPS-01 (SAS Protein Reference Unit, Sheffield, UK).

IgG4 concentrations were measured by a competitive inhibition enzyme linked immunosorbent assay (ELISA), which is described in greater detail elsewhere.[12] Briefly, plates were coated with a 1 in 250 dilution of a monoclonal anti-IgG4 antibody (MAb clone RJ4; Unipath Ltd, Bedford, UK). Two dilutions of the patient's serum were added to the plate in competition with a fixed amount of biotinylated IgG4 myeloma protein. The amount of biotinylated myeloma protein bound (which varies inversely with the IgG4 content of the patient's serum) was detected by avidin coupled to peroxidase. The plates were developed with 1 mM ABTS substrate containing 0·1 mM H_2O_2 and read using a Multiskan plate reader (Flow Labs, UK). The standard curve was made with doubling dilutions of known amounts of unlabelled IgG4 myeloma competing with the labelled version of itself.

Serum electrophoresis

Serum electrophoresis was performed using the Hiphore kit (Gelman Sciences, UK).

Identification of antinuclear antibodies

Antinuclear antibodies (ANAs) were detected by indirect immunofluorescence using HEp_2 cells as substrate.[13]

Detection of antibodies to extractable nuclear antigens

Antibodies to extractable nuclear antigens (ENAs) were detected by counterimmunoelectrophoresis.[14]

Measurement of antigammaglobulin antibody concentrations

Antigammaglobulin antibody (rheumatoid factor) concentrations were measured by two commercial kits: RAHA (Fujirebio, Japan) and Latex (Wellcome Diagnostics, UK).

Measurement of anti-double-stranded DNA antibodies

Anti-double-stranded DNA (anti-dsDNA) antibodies were measured using a modification of the ELISA method described elsewhere.[15] Antibody levels were estimated relative to a positive reference serum and expressed in arbitrary units/ml, taking levels of greater than 30 units/ml as being suggestive of SLE in this laboratory.

Table 1 *Serum immunoglobulin and IgG subclass concentrations (g/l) of 16 patients with a disproportionate polyclonal increase in IgG1*

Patient No	*IgG (6–18)**	*IgA (0·6–3·3)*	*IgM (0·4–1·5)*	*IgG1 (4–12)*	*IgG2 (1·5–7)*	*IgG3 (0·1–2)*	*IgG4 (0·04–2·7)*	*IgG1/IgG2 (0·57–8·0)*
1	19·2	3·4	0·5	22·0	1·6	0·4	0·5	13·8
2	32·0	4·5	2·2	29·0	2·4	1·1	1·5	12·1
3	23·0	1·7	1·6	27·0	1·1	0·3	<0·1	24·6
4	18·8	2·7	1·9	21·0	1·6	0·5	0·9	13·1
5	38·0	2·9	2·1	39·0	2·5	1·1	0·8	15·6
6	18·2	1·6	2·0	15·6	1·2	0·7	0·5	13·0
7	36·0	2·6	3·6	26·0	0·9	1·0	0·5	28·9
8	52·0	0·7	2·8	56·0	1·6	0·2	<0·1	35·0
9	40·0	2·2	1·9	42·0	0·3	0·3	0·2	140·0
10	58·0	2·0	1·6	52·0	1·4	1·3	0·1	37·1
11	48·0	2·1	1·5	50·0	1·6	0·5	0·2	31·3
12	26·5	1·6	1·7	26·5	1·0	0·6	<0·1	26·5
13	66·0	2·5	2·9	55·0	4·9	0·7	1·4	11·2
14	21·0	2·5	1·5	15·2	1·0	0·8	<0·1	15·2
15	35·0	1·9	2·5	27·0	1·9	0·5	<0·1	14·2
16	42·0	3·6	0·7	40·0	3·7	0·6	0·7	10·8

*Normal ranges are shown in parentheses.

STATISTICAL ANALYSIS

The Wilcoxon rank sum test and the χ^2 test were used when appropriate. A p value of <0·05 was taken as the minimum level of significance.

Results

Of 600 patients in whom we measured the IgG subclass concentrations between 1983 and 1986, we found 16 with a disproportionate increase in their serum IgG1 immunoglobulins but without a paraprotein. The other IgG subclasses, and in particular IgG2, were either reduced or at the lower end of the normal range, so that IgG1 concentrations were at least 10 times greater than those of IgG2 (Table 1). These patients, therefore, form a distinct group when the concentrations of these two immunoglobulins are plotted against each other ($p<<0·001$) (Fig. 1). The increase in the IgG1 subclass resulted in a raised total IgG, but IgA and IgM concentrations were normal. Eleven of the 16 patients were tested repeatedly for up to three years and gave consistent findings: the concentration of IgG1 either remained high or rose higher except when the patient was treated with prednisolone (>30 mg daily) or azathioprine (>100 mg daily).

Fourteen of the 16 patients were female. There appeared to be a characteristic pattern of autoantibodies (Table 2). Of the 13 patients tested for rheumatoid factor, 11 had high titres. ANAs were detected in all 14 patients tested, with a titre of 300 or greater in all but one case. Antibodies against ENAs were found in 13 of the 15 patients tested, and precipitins to Ro, La, and RNP antigens predominated. Anti-dsDNA antibodies (>10 U/ml) were detected in 10 of the 15 patients tested, but only three of them had levels over 30 U/ml suggestive of SLE.

Retrospective clinical review of the case notes showed that 14 patients had presented with symptoms suggestive of a connective tissue disorder. According to American Rheumatism Association criteria,[16 17] eight of these were classified as suffering from SLE and two from rheumatoid arthritis (RA). Two

Table 2 *Autoantibody profiles in the 16 patients with IgG subclass imbalance*

Patient No	*Age*	*Sex*	*ANA**		*ENA†*	*dsDNA (U/ml)*		*RF (titre)*		*Diagnosis*
			*Pattern**	*Titre*		*IgG*	*IgM*	*RAHA*	*Latex*	
1	58	F	spk	1000	Ro La	<10	<10	<8	<32	SLE
2	50	F	hom	1000	Neg	34	36	>256	>64	SLE
3	68	F	atp	1000	Neg	<10	<10	ND	ND	SLE
4	17	M	ND	ND	ND	ND	ND	ND	ND	Eczema
5	24	F	spk	1000	Ro La	15	22	>256	>64	SLE
6	68	M	hom	1000	Ro La	<10	<10	128	32	RA
7	49	F	hom	1000	Ro La	20	<10	>256	>64	SS†
8	52	F	spk	1000	Ro La	<10	13	>256	>64	SS
9	65	F	nc spk	1000 300	RNP	<10	<10	>256	>64	RA
10	36	F	hom	300	Ro La RNP	44	15	>256	>64	MCTD†
11	21	F	spk	300	Ro La	<10	15	128	64	SLE
12	33	F	spk	300	Ro La	<10	25	>256	>64	SLE
13	85	F	ND	ND	RNP	225	130	ND	ND	SLE
14	30	F	spk	1000	Ro La	<10	<10	>256	64	MCTD
15	31	F	spk nc	30 30	Ro La	<10	12	>256	64	SLE
16	30	F	spk nc	>1000 >1000	RNP	12	<10	<8	<8	SLE

*ANA=antinuclear antibody; spk=speckled; hom=homogeneous; atp=atypical; nc=nucleolar; Neg=negative; ND=not done.
†ENA=extractable nuclear antigen; SS=sicca syndrome; MCTD=mixed connective tissue disease.

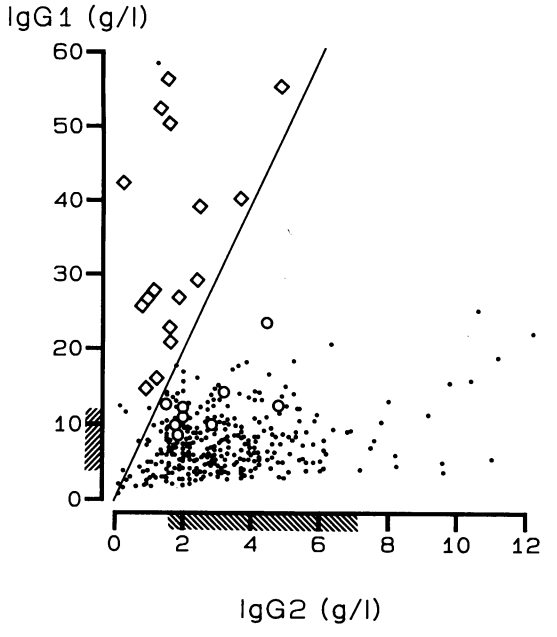

Fig. 1 *Distribution of serum concentrations of IgG1 against IgG2 in the 600 patients who underwent IgG subclass estimations between 1983 and 1986. Special symbols highlight patients with an IgG1 imbalance (◇) or hypergammaglobulinaemic patients with SLE without an IgG subclass imbalance (○). The stippled areas on the axes denote the normal ranges of IgG1 and IgG2. The oblique line shows where the concentration of IgG1 is 10 times greater than that of IgG2, so any point to its left denotes a ratio of greater than 10:1. The patients without the above IgG subclass imbalance who lie to the left of this line are either IgG2 deficient or have an IgG1 paraprotein.*

patients were diagnosed as mixed connective tissue disease (MCTD) and two as primary sicca syndrome (SS). Of the remaining two patients, one presented with atopic eczema and had high concentrations of both IgE and anti-IgE antibodies; the sixteenth patient presented with urticaria and angioedema. This last patient developed a photosensitive rash with skin biopsy specimen characteristic of SLE some 18 months after the immunological abnormalities were noted. Thus 15 of 16 patients had a CTD. By way of comparison, in a group of 33 patients selected for raised total IgG but no IgG1:IgG2 imbalance, only 21 (64%) had a CTD (Table 3).

The immunological abnormalities appeared to cut across the usual diagnostic categories. To make some comparison of the prevalence of autoantibodies in patients with and without the IgG subclass imbalance we selected patients with SLE as these formed the largest subset from each group. Among these patients, ANAs in high titre, rheumatoid factor in high titre, and anti-ENA antibodies were all more prevalent in those with IgG1 imbalance than in patients with SLE from the comparison group (Table 4). High levels of anti-dsDNA were more prevalent in the hypergammaglobulinaemic SLE comparison group.

Table 3 *Clinical diagnoses in the 16 patients with disproportionate polyclonal IgG1 concentrations and 33 patients similarly hypergammaglobulinaemic without IgG subclass imbalance*

	Raised IgG IgG1/IgG2>10	*Raised IgG IgG1/IgG2<10*
With CTD*	SLE (9)	SLE (9)
	RA (2)	RA (9)
	MCTD (2)	MCTD (1)
	SS (2)	Eosinophilic faciitis (1)
		PBC* (1)
Without CTD	Eczema (1)	Respiratory tract infection (6)
		Urticaria (3)
		Coeliac disease (1)
		Chronic granulomatous disease (1)
		Chronic renal failure (1)

*CTD=connective tissue disease; PBC=primary biliary cirrhosis.

Table 4 *Autoantibody findings in nine patients with SLE with a disproportionate increase in IgG1 and nine similarly hypergammaglobulinaemic patients with SLE without an IgG subclass imbalance*

Result	*Patients with SLE and IgG subclass imbalance*	*Hypergammaglobulinaemic controls with SLE*
ANA titre≥300	7/8	5/9
ANA pattern*		
spk	6/8	3/9
nc	2/8	2/9
hom	1/8	3/9
atp	1/8	0/9
RF titre		
RAHA>64 / Latex>32	5/7	0/8
dsDNA level		
>30 U/ml	2/9	6/9
ENA +ve	7/9	5/9
RNP +ve	2/9	0/9
Ro or La +ve, or both +ve	5/9	4/9
Jo-1 +ve	0/9	1/9

*For abbreviation see Table 2.

Discussion

Our computerised filing system[18] has enabled us to identify an unusual subset of patients who have a distinctive immunoglobulin imbalance. One patient with a very high concentration of polyclonal IgG1 initially alerted us to the phenomenon. When the abnormality was defined as a raised concentration of IgG1, with an IgG1:IgG2 ratio of 10:1, a search of our data files disclosed 15 more patients with this pattern of results. These patients not only had the IgG subclass imbalance but also a distinct autoantibody pattern with high titres of ANAs and rheumatoid factor and the presence of anti-ENA antibodies in most cases. The prevalence of CTD was about twice that of other patients with a similarly raised immunoglobulin G concentration without the subclass imbalance. Studies are underway to ascertain the overall prevalence of this subclass imbalance in CTD. In one patient presenting with urticaria and angiodema the immunological abnormalities were detected some 18 months before SLE became clinically apparent. We have heard of two nephritic patients who had high concentration of IgG1 before the development of Sjögren's syndrome. Thus IgG subclass imbalance, though spanning the usual clinical subdivisions, may be an early indication of CTD in evolution.

The precise cause of B cell overactivity in CTD is unknown but among the possibilities are genetic factors, unidentified polyclonal B cell activators, and defective immunoregulation.[1] Most studies of SLE in both humans and mice have found defective suppressor function,[19–23] but in the MRL mouse model there is excessive helper cell activity.[5] Increased lymphocyte transformation and lymphokine production in cartilage-type proteoglycan and collagen derived antigens have been described in a range of connective tissue disorders,[24] and animal studies have shown that effector and helper T cell functions may be mediated by the same cell.[25 26]

Aberrant T helper cells have shown to be responsible for the abnormally high concentrations of IgG and IgA in a patient with Sézary's syndrome; these cells induced the secretion of IgG and IgA by B cells from a patient deficient in these immunoglobulins (hyper-IgM immunodeficiency) and produced similar effects when cocultured with B cells from normal subjects.[27] Studies using murine cell lines have demonstrated T cells which stimulate the secretion of IgG1 by B lymphocytes via the release of a lymphokine,[28–30] and recent data suggest that in some murine models of SLE isotype-specific as well as antigen-specific T helper cells may be increased.[31] One possibility, therefore, is that an IgG1-specific lymphokine is responsible for the abnormality in our patients.

The defective immunosuppression found in patients with SLE has been most commonly attributed to autoantibodies directed against the patients' suppressor T cells.[32–35] Not all the antilymphocytic antibodies found in SLE are inhibitory, however, and there is a report of SLE antibodies causing activation of lymphocytes in culture.[36] Hence it may be an autoantibody that is responsible for the increased IgG1 production, either by stimulating the isotype-specific helper T cell or by acting on B cells directly. In our patients with IgG subclass imbalance we have preliminary data suggesting that there is a serum factor capable of selectively enhancing IgG1 production by normal splenocytes in vitro.

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