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DYSGAMMAGLOBULINAEMIA TYPE IV C

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SUMMARY

Two further patients with isolated deficiency of serum γA-globulin, low normal γG-globulin and increased γM-globulin are described. Following antigenic challenge very little antibody activity could be detected in their sera. No defect of cellular immunity was shown.

Associated autoimmune haemolytic anaemia and thrombocytopenic purpura were improved by corticosteroid therapy and in one case by splenectomy.

The immunoglobulin pattern is unusual in adults and may be diagnostic of dysgammaglobulinaemia.

INTRODUCTION

The antibody deficiency syndromes can be classified into two groups: (1) the hypogammaglobulinaemias in which the deficiency of γ-globulin and, therefore, of antibodies can be diagnosed by simple serum electrophoresis; and (2) the dysgammaglobulinaemias in which the γ-globulin is apparently normal on electrophoresis and only testing for specific antibodies or measuring the levels of the different immunoglobulins reveals any defect.

Because normal responses to antigens vary so widely, dysgammaglobulinaemia is difficult to diagnose. It is necessary to test a whole range of antigens, using a primary challenge and booster doses. Alternatively it is easier to measure serum immunoglobulins quantitatively. Nine patterns (see Table 1) are known to be associated with dysgammaglobulinaemia and one (IV C) has recently been described in this journal by Dr R. T. Williams.

Two further patients with the same pattern (IV C) are described here. So far, all the patients that have been described as having increased γM levels, severe reduction of γA levels and low normal (IV C) or very low γG levels (II) in their serum, have had symptoms of antibody deficiency. In contrast, four of the other patterns (III O, IV O, V O and VI O) can be found in the serum of healthy subjects.

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TABLE 1. Serum immunoglobulin levels in idiopathic antibody deficiency syndromes. Most have a familial and probably a genetic background, except where indicated (T) and sub-types O (no demonstrable antibody deficiency syndrome) are included to show that these immunoglobulin patterns alone are not diagnostic

Immunoglobulin			γG (mg/100 ml)	γA (mg/100 ml)	γM (mg/100 ml)	References
Mean levels of 107 normal adults			1000	260	100	i.e. 100% RNS
Adult normal ranges (skew)			600–1600	125–425	50–170	21
Hypogammaglobulinaemia						
T	From soon after birth	Sex linked recessive	<200	<20	<50	16
T	From soon after birth	Non sex linked*	<100	<10	<5	16
T	From soon after birth	Non sex linked with achondroplasia*	<100	<10	<5	7
T	From soon after birth	Acquired *in utero* (rubella)*	<200	<10	<20	34, 29, 35, 30
	Acquired in adult life		<200	<100	<50	16, 5, 13, 39, 40
T	Truly acquired as adult		<200	<100	<50	20
Dysgammaglobulinaemia						
Type I	Deficiency γA, γM		490–1000	<20	<10	
A	From birth					14, 3
B	Acquired as adult					15
Type II	Deficiency γG, γA, High γM‡					
A	From birth		<200	<20	70–1000	26, 27, 33, 23, 25, 36
T	Acquired in utero (rubella)*		<200	<50	175–2000	35
B	Acquired as adult		50	<20	<200	32

Type III	Isolated deficiency γG	400	125–425	50–170	
O	Asymptomatic relatives				5
A	Acquired				17
Type IV	Isolated deficiency γA				
O	Healthy	600–1600	<20	50–170	18, 37, 39, 5, 31, 2, 30
A	85% Ataxia telangiectasia*, sino-respiratory infection	200–1600	<20	50–170	29, 12, 4
B	Other symptoms, idiopathic steatorrhoea, fatal haemorrhagic varicella†	500–1600	<20	50–170	9, †2 personal patients
C	With raised γM‡	400–1000	<20	135–600	38, 19, Present patients
Type V	Isolated deficiency γM				
O	Healthy	600–1600	125–425	<50	39, 40, 5
A	With raised γA, Aldrich syndrome	600–1600	250–600†	<10–70	1, 36 †Markedly raised for age
B	Septicaemia	500–1800	100–425	<10	22
Type VI	Apparently normal levels				
O	Normal population	600–1600	125–425	50–170	
A	Symptomatic in later life	400–1000	140–240	50–75	20, 8 A third patient seen recently
Type VIII	Deficiency γG, γM, high γA				
A	From birth	<200	1–2000	<20	5a, 1 personal patient

Dysgammaglobulinaemia types have been numbered in chronological order, thus I, II agree with Gilbert & Hong (1964) but II is called I by 25, 36.

* May also have defects of cellular immunity.

‡ The γM may or may not possess demonstrable antibody activity, e.g. isoagglutinins.

Case Reports

Patient 1

In February 1961 a 44-year-old housewife developed acutely a severe autoimmune haemolytic anaemia, which responded well to treatment with prednisone (Fig. 1). At that time her platelet count was normal and she showed no haemorrhagic tendency. The steroid was gradually reduced and in February 1962 discontinued altogether. In April 1962 she developed a skin infection of the lower part of the abdomen, vulva and buttocks, which was treated by her own practitioner. In June, when this was clearing up, she developed a fever and purpuric rash. Her platelet count was now found to be low (30,000/mm^3) and she was given prednisone, which resulted in a prompt rise in the platelet count.

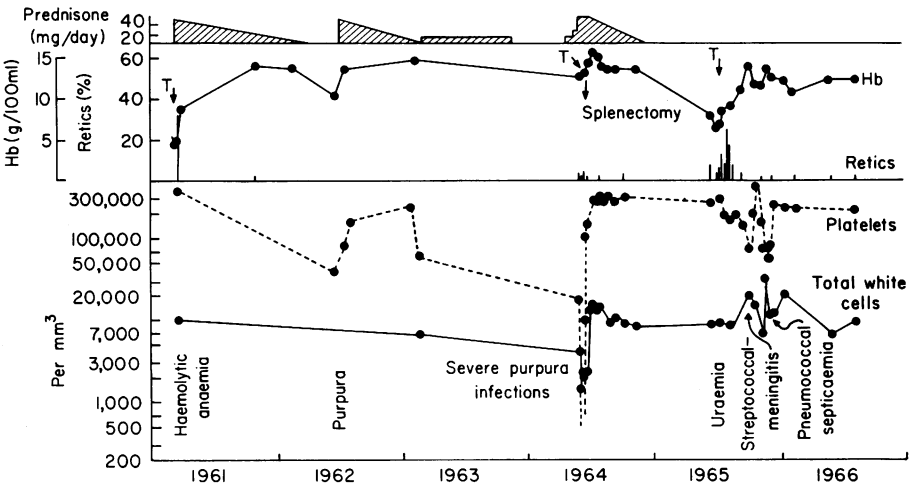

FIG. 1. Chart showing the salient clinical features and haematological findings in patient 1 in relation to corticosteroid therapy and splenectomy.

In January 1963 the prednisone was again withdrawn but this resulted in a fall in her platelet count to 60,000/mm^3, so she was started again on a small dose of corticosteroids, which kept her platelet count at about 100,000/mm^3.

In June 1963 she had an episode that was thought to be due to a small cerebral haemorrhage. She was admitted to the Atkinson–Memorial Hospital; the platelet count was normal and she made a good recovery, but the corticosteroid was discontinued.

In May 1964 she developed bruising all over the body following a sore throat She recovered from this, but in June 1964 she had a sore throat again and this was followed by an infection of a pin prick of her finger, and she subsequently developed widespread bruising and purpura. She was admitted with a severe thrombocytopenia and leucopenia, though her haemoglobin was over 12 g/100 ml and the reticulocytes were 4%. The marrow biopsy showed numerous megakarocytes and after intensive therapy with antibiotics, prednisone and ACTH, her platelet count rose and she improved. It was then decided to perform a splenectomy and at the end of June 1964 a 290 *g* spleen was removed. The corticosteroid was gradually reduced and in November 1964 discontinued altogether, since when her haemoglobin and platelet count have been fairly satisfactory.

She remained well until March 1965 when she developed a nasal discharge. In April she started vomiting and this continued until June when she was re-admitted with acute renal failure (blood urea 295 mg/100 ml) for which no cause could be found and from which she gradually recovered without specific therapy, but her blood urea has since remained elevated (55–95 mg/100 ml).

In October 1965 she developed severe meningitis and a non-haemolytic streptococcus Lancefield Type D was isolated from her CSF. She made a good recovery from this but in November 1965 she was again re-admitted with pneumococcal septicaemia. She again responded to antibiotics, but in view of these two severe infections, prophylactic tetracycline, 500 mg daily, was commenced and she has remained well except for an episode of purulent bronchitis lasting 4 weeks in May 1966.

Patient 2

A girl of 2½ years, previously well, developed jaundice and hepatosplenomegaly in March 1959. Her jaundice was found to be due to autoimmune haemolytic anaemia and her red cells appeared to be coated with a γG-antibody despite mild hypogammaglobulinaemia. Her anaemia responded well to prednisolone but on its withdrawal in October 1960, she developed fever, lumps in muscles, severe peripheral neuritis and increased jaundice. Further prednisolone enabled her to maintain her haemoglobin between 9·0–13·0 g/100 ml and her reticulocytes between 14–40% but she developed a persistent productive cough and clubbing of her fingers. The corticosteroids had to be continued and the bronchitis, which was accompanied by purulent sputum containing a sequence of pyogenic organisms, never responded completely to antibiotics and physiotherapy.

At necropsy, cytomegalic pneumonia was found; there was little structural alteration in the bronchi but widespread granulomatosis throughout the lymph nodes and liver. Plasma cells were present and appeared normal in morphology but the follicles of the lymph nodes showed a striking lack of hyperplasia when contrasted with the general lymphoid hyperplasia of the cortex.

LABORATORY RESULTS

Patient 1

Serum immunoglobulins

These were estimated by a modified Mancini method (Hobbs & Maatela, to be published). Sera dating from 1961 and stored at −20°C were used. Such sera, provided the aliquots have been thawed only once, have been shown to give reliable results; the immunoglobulin levels of our own reference normal serum having fallen <10% in 4 years.

Date	γG (mg/100 ml)	γA (mg/100 ml)	γM (mg/100 ml)
13 March 1961	520	60	120
29 July 1962	660	35	420
11 February 1963	600	38	200
8 July 1965	1200	21	500
23 November 1965	500	25	480
1 December 1965	1000	38	600
8 February 1966	800	19	260
31 May 1966	550	21	175
13 September 1966	540	14	135
16 November 1966	500	24	200
Normal range	600–1600	125–425	50–175

Blood group

ABO	*Rh phenotype*	*MN*	*S*	P_1	Lu^a	*K*	Le^a	Le^b	Fy^a
O	CcDee	MN	+	+	−	−	−	−	−

Titres

Anti-A: 16, anti-B: 1.

Direct antiglobulin test and autoantibody in the serum

The red cells were agglutinated by anti-γG-globulin and not by anti-complement. The antibody eluted off the red cells showed some anti-c specificity. Autoantibody was detectable in the serum to a titre of 64 and showed some anti-c specificity.

Antibody studies

Response to oral poliomyelitis vaccine (Dr A. J. Beale, Glaxo Laboratories Ltd). Samples of blood were taken before the vaccine was administered and 3 weeks after the first and second challenge doses (3 drops of vaccine). Standard neutralization tests were carried out and the end-point of the cytopathic effect is given below. The initial samples showed appreciable cytopathic effects but this was not increased by the vaccine.

	Before		After (1)	After (2)
Polio I	1/32	1/48	1/32	1/32
Polio II	1/32	1/48	1/32	1/32
Polio III	1/16	1/32	1/16	1/16

Response to Brucellin (Mr R. Lambert, Royal Postgraduate Medical School). Parke–Davis Brucellin was used and agglutination titres were measured before and 3 weeks after the first and second challenge doses of 0·5 and 1·0 ml, respectively. The titrations were taken to titre of 4096 to exclude false negative results due to 'blocking' antibody but no agglutination was found either before or after the injections.

Response to tetanus toxoid (Dr Weitz, Lister Institute). Less than 1/80 of an international unit of tetanus antitoxin was found before inoculation with tetanus toxoid and there was no response to two injections, each of 1 ml.

Lymphocyte transformation (Dr C. Pentycross, during tenure of Leukaemia Research Fund Ltd grant, Royal Marsden Hospital). The number of cells transformed by the antigen are given as a percentage in the table at the head of p. 595.

	Before	After first challenge	After second challenge (A.R., Guy's Hospital)	Normal ranges
Polio antigen	0	0	2	3–7
Brucella antigen	0	1·2	1–2	10–20
Tetanus antigen	0	0	5	10–20
Phytohaemagglutinin	11	48*	64	80–95

* Normal range 30–55.

Chromosome studies (Dr S. Lawler, Royal Marsden Hospital)

Studies of peripheral blood lymphocyte cultures were done on two occasions and no abnormality was found. The additional chromosome described by Williams (1966) was not seen.

Family studies

The patient's father had died of Bright's disease at the age of 42 and her mother had died of heart failure at the age of 80. There was no history of undue susceptibility to infections in any member of the family. One brother, aged 48, and the son and daughter of the patient, aged 16 and 19 years respectively, are alive and well. Their serum immunoglobulin levels are given below in mg/100 ml.

	γG	γA	γM
Brother	1000	600	45
Son	740	160	55
Daughter	1050	350	90

Patient 2

Serum immunoglobulins (Dr J. F. Soothill, Birmingham)

March 1956 Low γ
November 1960 Low γ
October 1961 0·4g γ/100 ml
} by electrophoresis.

Date (1962)	γG (mg/100 ml)	γA (% RNS)*	γM (% RNS)*
15 January	640	0.1	100
12 January†	1600	0·1	400
20 January†	2560	0·2	300
Normal range	600–1600	48–164	50–170

* RNS, Reference normal serum.

† At the time of a staphyloccocus pyogenes exacerbation of the bronchitis.

Blood group

ABO	*Rh phenotype*	*MN*	*S*	P_1	Lu^a	*K*	Le^a	Le^b	Fy^a
A_1	ccDEE	MN	−	+++	−	/	−	−	/

Isoagglutinin titres were not done.

Direct antiglobulin test and autoantibody in the serum

The red cells were agglutinated by anti-γG-globulin and not by anti-complement. Very little autoantibody was detected in the serum and an eluate was not made.

Antibody studies

Triple antigen had been given on three occasions. The Schick test was negative and only 0·001–0·01 units/ml of diphtheria antitoxin were detected.

DISCUSSION

The case reports and laboratory results offer reasonable evidence of an antibody deficiency syndrome in both patients.

Secondary or idiopathic?

In patient 1 observations over 6 years and in patient 2 necropsy has not revealed any underlying neoplasia within the reticulo-endothelial system and other known causes of secondary antibody deficiency (Hobbs, 1966) have been excluded. Furthermore, personal (J.R.H.) experience of over 400 patients with secondary deficiencies has shown that the fall in γM level usually precedes the fall in γA level, which itself only rarely falls below 20 mg/100 ml. When, however, γA levels are very low, γG levels will usually have also fallen into the hypogammaglobulinaemia range of below 200 γg/100 ml. The present immunoglobulin pattern may be found in neonates but has not been encountered in adults or children over 4 years of age and is presumably idiopathic in origin.

Genetic or truly acquired?

Antibody deficiency syndromes becoming symptomatic soon after birth may be genetic in origin (Good *et al.*, 1962) or acquired *in utero* (Soothill, Hayes & Dudgeon, 1966; Plotkin, Klaus & Whitely, 1966). Similarly, those first presenting in later life may have a clear genetic background (Wollheim *et al.*, 1964) or be truly acquired (Hobbs, 1966).

In general, dysgammaglobulinaemia with a genetic basis will be found to be accompanied by isolated defects of serum immunoglobulins among the relatives, many of whom may be symptomless. The brother of patient 1 shows a raised serum γA level as did some of the relatives described by Burtin, Buffe & Graber (1966). Isolated γA deficiency has been described as occurring in 1:700 of normal subjects (Bachmann, 1965), in association with

ataxia telangectasia and a predisposition to sino-pulmonary infections (see Table 1), or associated with steatorrhoea (Crabbe & Heremans, 1966).

The patients described here and the patient of Williams show a new association, for apart from autoantibody, no new antibody response could be elicited in spite of the fact that in all three cases the γG level was around the lower limit of normal (600 mg/100 ml). In other patients, the failure of the γ-globulin as demonstrated by electrophoresis, to rise in response to infections, has been a useful pointer to dysgammaglobulinaemia. However, in these patients γG and γM levels rose after infection, indicating that they can make these immunoglobulins, but without any demonstrable antibody activity. This may possibly be due to a defect in the synthesis of antigen binding sites or to interference with the ability of the antibody to bind antigen.

Autoimmune aspects

Autoimmune haemolytic anaemia in association with hypogammaglobulinaemia has been described by Fudenberg & Solomon (1961) but in their cases and in four additional patients of Professor Dacie, the present dysgammaglobulinaemic pattern was not found. The patient of Hinz & Boyer (1963) gave an identical pattern but no evidence of antibody deficiency or infection was recorded and their patient resembles patient 1 when she first presented. In the patient of Williams, mild unexplained haemolysis was present. Some evidence that the antibody deficiency itself may be the result of autoimmune phenomena has been put forward by Soothill (1967) and perhaps this may be the underlying cause in our patients. There is an excellent precedent in pernicious anaemia to explain how a hereditary defect could become manifest in adult life. However, in neither of these patients did the γA level rise or antibody activity appear following large doses of corticosteroids as happened in the patient described by Soothill.

The role of the spleen

It seems possible that the splenic hyperplasia commonly seen in adult acquired antibody deficiency syndromes (Citron, 1957) improves the patient's response to infections. At the same time any haemolytic or thrombocytopenic tendency would be aggravated. Patient 1 had suffered no severe infections until 1962 even though the immunoglobulin pattern was already extant. Repeated severe infection frequently follows splenectomy (Lowdon, Stewart & Walker, 1966) especially in the first years of life (Horan & Colebatch, 1962; Ellis & Smith, 1966), but not usually in adult (Doan, Bruce & Wiseman, 1956). Splenectomy in adults with antibody deficiency syndromes, however, may increase the risk of blood-borne infections and this seems to have happened to patient 1 although her haemolysis and thrombocytopenia were improved by the operation.

Significance of the immunoglobulin pattern

It is of interest that during human immunological maturation, serum γM-globulin levels rise first, then γG and then γA (West, Hong & Holland, 1962). We have seen the present pattern in infants with infections, although usually the γA-globulin shows some increase over the initial level. If maturation were to fail at a late stage this pattern could become fixed but in neither of our patients is there evidence of its presence since birth.

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