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HUMAN ANTI-IgM ISO-ANTIBODIES IN SUBJECTS WITH SELECTIVE IgA DEFICIENCY

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SUMMARY

IgG-class iso-antibodies against human IgM ('reverse rheumatoid factors') were detected in titres from 1:4 to 1:1024 in the serum of twelve of forty subjects (30%) with selective IgA deficiency. The antibodies were detected in a haemagglutination system with red cells coated by the chromic chloride method with proteins from a panel including nineteen Waldenström macroglobulins. The forty subjects included seventeen normal subjects, ten with recurrent infections, seven with ataxia telangiectasia, two each with asthma and lymphoma and one each with rheumatoid arthritis and chronic active hepatitis. Four of the twelve positive sera contained 'class-specific anti-IgM' which reacted with all or most of the IgM coats. The eight sera containing 'anti-IgM of limited specificity' included six reacting with only one IgM coat, one reacting with two IgM coats and one reacting with four IgM coats. The anti-IgM in the latter serum defined an inherited allotypic marker on these four IgM proteins. There was no significant correlation between the presence of anti-IgM antibodies and the clinical status, sex and age of the patient nor the presence of antibodies against human IgG, human IgA and ruminant proteins. These antibodies against human IgM represent yet another immunologic abnormality in this group of patients.

INTRODUCTION

Selective deficiency of serum IgA occurs in 0·2–0·3% of Caucasian subjects in population surveys and is the most frequently observed immunoglobulin deficiency (Bachmann, 1965; Huntley & Stephenson, 1968; Collins-Williams *et al.*, 1972). Although it may frequently be noted in individual subjects who are apparently clinically normal (Collins-Williams *et al.*, 1972; Goldberg, Barnett & Fudenberg, 1968), studies of larger groups of subjects with selective IgA deficiency demonstrate its association with a high incidence of auto-immune diseases, auto-antibodies without apparent disease and gastrointestinal disorders (Tomasi, 1968; Claman *et al.*, 1970; Ammann & Hong, 1971). Serological abnormalities are frequently

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detected in selective IgA deficiency, including antibodies against human IgG, human IgA, bovine IgM, bovine milk, goat serum, human thyroglobulin and various human tissue antigens (Fudenberg *et al.*, 1968; Goldberg, Barnett & Fudenberg, 1968; Tomasi, 1968; Buckley & Rees, 1969; Claman *et al.*, 1970; Vyas & Fudenberg, 1970; Amman & Hong, 1971; Fudenberg & Vyas, 1971; Huntley *et al.*, 1971; Leikola & Vyas, 1971; Tomasi & Katz, 1971).

Earlier studies from this laboratory had noted serum antibodies to human IgM in both normal subjects and after multiple blood transfusions or multiple pregnancies (MacKenzie, Mackey & Fudenberg, 1967; Leikola *et al.*, 1971). Recently we studied a serum (1. R.K.) containing anti-IgM antibodies which defined the first reported allotype or inherited antigenic marker on human IgM-Im μl (Wells, Bleumers & Fudenberg, 1972). Since subject 1. R.K. is an asymptomatic normal female with selective IgA deficiency, anti-IgM antibodies have been sought in other subjects with this abnormality. This paper presents data on IgG antihuman IgM antibodies ('reverse rheumatoid factors') detected in 30% of a series of forty subjects with selective IgA deficiency.

MATERIALS AND METHODS

Subjects

Selective IgA deficiency was defined as a serum IgA level undetectable by routine immunodiffusion (<3 mg/100 ml) with normal or increased serum levels of IgG and IgM. Table 1 lists the clinical and laboratory data for the forty subjects. Several of the serum specimens were referred for study from physicians in the U.S.A. and Australia and were not personally investigated by us for clinical and laboratory abnormalities apart from the serological studies. Several subjects were detected with selective IgA deficiency during family studies of patients with adult acquired hypogammaglobulinaemia.

Techniques

Serum levels of IgG, IgA and IgM were measured by radial immunodiffusion in antiserum-agar plates (Mancini, Carbonara & Heremans, 1965). Precipitating antibodies against ruminant proteins (normal goat serum and bovine IgM) were detected in IgA-deficient sera by double-diffusion in 1·5% agar with 0·025 M barbital buffer, pH 8·6 (Huntley *et al.*, 1971). Serum antibodies against human IgG, IgA and IgM were detected by haemagglutination with human 0+ red cells coated by the chromic chloride method (Vyas *et al.*, 1968) with purified proteins from a test panel including nineteen Waldenström macroglobulins (Table 3). The proteins in the test panel were isolated by standard immunochemical methods from human sera with DEAE-cellulose chromatography (0·015 M phosphate buffer, pH 7·8), euglobulin precipitation, starch block electrophoresis, and gel filtration on Sephadex G-200; or from urine by ammonium sulphate precipitation (33% saturation) and gel filtration on Sephadex G-75 (Leikola *et al.*, 1971). The immunologic purity of all proteins was confirmed by Ouchterlony double diffusion or immunoelectrophoresis in agar with monospecific antisera. Where sufficient serum was available from an IgA-deficient subject with serum anti-IgM antibodies, the specificities of the antibodies were investigated by testing for inhibition by the proteins in solution.

RESULTS

Clinical and laboratory data

The data for the forty subjects are listed in Table 1. Seventeen subjects (43%) were clini-

TABLE 1. Summary of clinical and laboratory data on forty subjects with selective IgA deficiency

Subject	Sex	Age (yr)	Clinical features	Serum immunoglobulins (mg/100 ml)*		Serum antibodies against			
				IgG	IgM	Human IgG	Human IgA	Human IgM	Ruminant proteins
1. R.K.	F	30	Normal	1480	300	−	−	+	−
2. H.R.+	F	73	Normal	1200	54	−	−	−	−
3. P.R.+	F	20	Normal	1650	414	−	−	+	−
4. R.R.+	F	17	Normal	1000	216	−	−	−	−
5. K.R.	F	16	Normal	2100	56	−	−	−	+
6. J.R.	F	13	Recurrent infections	1600	56	−	−	−	−
7. L.C.	F	58	Asthma	1310	153	−	−	−	−
8. W.M.	F	18	Normal	1490	137	−	−	−	+
9. F.C.	F	42	Transfusion anaphylaxis	664	52	−	+	−	+
10. M.P.	F	31	Chronic active hepatitis	1500	165	+	−	+	−
11. L.D.	F	38	Normal	885	75	−	+	−	−
12. M.H.	F	40	Normal	790	80	−	+	−	−
13. D.S.	F	23	Recurrent infections	626	132	−	+	−	−
14. E.R.	F	4	Recurrent infections	3100	145	−	−	−	+
15. M.E.	F	35	Normal	1190	125	−	+	+	−
16. P.R.	F	70	Lymphoma	560	48	−	−	−	−
17. A.B.	F	42	Normal	1450	195	−	−	−	+
18. W.M.	F	18	Normal	1490	137	−	−	−	−
19. E.F.	M	44	Diverticulitis, arthralgia	1850	110	−	−	+	+
20. R.C.	M	30	Recurrent infections	5000	83	−	−	−	−
21. R.V.	M	12	Normal	1450	95	−	−	+	−
22. J.S.	M	4	Normal	975	104	−	−	+	−
23. W.R.	M	40	Rheumatoid arthritis	1780	256	+	−	−	−
24. L.G.	M	46	Normal	2200	165	−	+	−	+
25. W.B.	M	38	Normal	1900	80	−	+	−	−
26. B.S.	M	3	Recurrent infections	1600	87	−	−	−	−
27. J.M.	M	29	Normal	2400	210	−	+	−	+
28. M.P.	M	30	Asthma	1200	270	+	−	−	−
29. J.W.	M	8	Recurrent infections	950	95	−	+	+	−
30. J.T.	M	6	Recurrent infections	910	80	−	+	+	+
31. C.S.	M	5	Recurrent infections	670	60	−	+	+	+
32. G.M.	M	16	Normal	950	110	−	+	−	−
33. J.B.	M	22	Lymphoma	1700	170	−	−	−	+
34. C.P.	M	4	Ataxia telangiectasia	810	63	−	−	−	+
35. M.P.	F	3	Ataxia telangiectasia	750	70	−	+	−	−
36. M.C.	F	3	Ataxia telangiectasia	550	50	−	+	+	−
37. F.R.	F	4	Ataxia telangiectasia	720	65	−	−	−	−
38. P.S.	F	13	Ataxia telangiectasia	1000	90	−	−	−	−
39. D.M.	M	6	Ataxia telangiectasia	2200	145	−	−	+	−
40. J.Z.	M	4	Ataxia telangiectasia	2110	94	−	+	−	−

* Normal levels in adults: IgG, 550–1600; IgM, 45–200 mg/100 ml.

+ 2 H.R. is the mother and 3. P.R. and 4. P.R. the daughters of a patient with acquired hypogammaglobulinaemia.

‡ Siblings.

cally normal; the other twenty-three subjects included nine with recurrent infections (23%), seven with ataxia telangiectasia (17%), two each with asthma and lymphoma, and one each with rheumatoid arthritis and chronic active hepatitis. Anti-IgM antibodies were detected in twelve subjects (30%), including five normal subjects, three with recurrent infections, two with ataxia telangiectasia and one each with rheumatoid arthritis and chronic active hepatitis. Antibodies to human IgG, human IgA and ruminant IgM were detected in three (8%), fifteen (38%) and twelve (30%) subjects respectively, but no correlation existed between their presence or absence and the presence of anti-IgM antibodies. The incidences of clinical and immunological abnormalities in subjects with or without serum anti-IgM antibodies are summarized in Table 2. There was no statistically significant correlation between the presence of anti-IgM antibodies in the serum of an individual subject and either their clinical status or the presence of other immunological abnormalities such as polyclonal increases in serum immunoglobulins.

Ten of the forty subjects had serum antibodies against more than one protein: two subjects with recurrent infections had antibodies against human IgA and IgM and ruminant IgM

TABLE 2. Comparison of clinical and immunological abnormalities with the presence or absence of serum anti-IgM antibodies in forty subjects with selective IgA deficiency

	IgA-deficient sera (40)		IgA-deficient sera without anti-IgM antibodies (28)		IgA-deficient sera with anti-IgM antibodies (12)	
Category	No.	(%)	No.	(%)	No.	(%)
Clinically normal	17	43	12	43	5	42
Recurrent infections	9	23	5	17	4	33
Ataxia telangiectasia	7	17	5	18	2	16
Polyclonal increase in IgG	12	30	9	31	3	25
Polyclonal increase in IgM	6	15	4	14	2	17
Antibodies to human IgG	3	8	2	7	1	9
Antibodies to human IgA	15	38	10	34	5	42
Antibodies to bovine IgM	12	30	9	32	3	25

(30. J.T.; 31. C.S.); one had antibodies against human IgG and IgM (10. M.P.); three had antibodies against human IgA and IgM (15. M.E.; 29. J.W.; 36. M.C.); three had antibodies against human IgA and ruminant IgM (9. F.C.; 24. L.G.; 27. J.M.); and one had antibodies against human and ruminant IgM (19. E.F.). Of the ten subjects with multiple antibodies, four had recurrent infections and three were clinically normal. The antibodies against ruminant IgM in 9. F.C.; 24. L.G. and 34. C.P. were previously reported (Leikola & Vyas, 1971).

Analysis of anti-IgM antibodies

Data on the agglutination of individual protein coats by the test sera are summarized in Table 3. The most frequently positive coat was pooled myeloma IgA which was agglutinated by fifteen serum specimens. Of the IgM protein coats: coat (7) reacted with nine sera, coat (10) reacted with six sera, coats (8) and (18) each reacted with five sera, twelve coats each reacted with four sera, and coats (12), (16) and (19) each reacted with three sera.

TABLE 3. Panel of proteins used as red cell coats and serum specimens containing antibodies against individual coats

Protein coat	Source (patient)	Light chain type	Subjects with serum antibodies against individual protein coats
(1)	Ca	κ	10. M.P.; 15. M.E.; 19. E.F.; 29. J.W.
(2)	Vi	κ	10. M.P.; 15. M.E.; 19. E.F.; 29. J.W.
(3)	Gr	κ	10. M.P.; 15. M.E.; 19. E.F.; 29. J.W.
(4)	St	λ	10. M.P.; 15. M.E.; 19. E.F.; 29. J.W.
(5)	Bo	κ	10. M.P.; 15. M.E.; 19. E.F.; 29. J.W.
(6)	Au	κ	10. M.P.; 15. M.E.; 19. E.F.; 29. J.W.
(7)	Gi	κ	1. R.K.; 3. P.R.; 10. M.P.; 15. M.E.; 19. E.F.; 21. R.V.; 22. J.S.; 29. J.W.; 39. D.M.
(8)	Pr	κ	1. R.K.; 10. M.P.; 15. M.E.; 19. E.F.; 29. J.W.
(9)	Bi	κ	10. M.P.; 15. M.E.; 19. E.F.; 29. J.W.
(10)	Pi	κ	1. R.K.; 10. M.P.; 15. M.E.; 19. E.F.; 29. J.W. 36. M.C.
(11)	Ka	λ	1. R.K.; 10. M.P.; 15. M.E.; 19. E.F.
(12)	Qu	λ	10. M.P.; 15. M.E.; 19. E.F.
(13)	Wm	λ	10. M.P.; 15. M.E.; 19. E.F.; 29. J.W.
(14)	Hi	κ	10. M.P.; 15. M.E.; 19. E.F.; 29. J.W.
(15)	Ti	κ	10. M.P.; 15. M.E.; 19. E.F.; 29. J.W.
(16)	Ha	κ	10. M.P.; 15. M.E.; 19. E.F.
(17)	Fr	κ	10. M.P.; 15. M.E.; 19. E.F.; 30. J.T.
(18)	Do	λ	10. M.P.; 15. M.E.; 19. E.F.; 30. J.T.; 31. C.S.
(19)	Ev	λ	10. M.P.; 15. M.E.; 19. E.F.
Normal IgG	Normal	κ λ	10. M.P.; 23. W.R.; 28. M.P.
Pooled IgA	Myeloma	κ λ	9. F.C.; 11. L.D.; 12. M.H.; 13. D.S.; 15. M.E.; 24. L.G.; 25. W.B.; 27. J.M.; 29. J.W.; 30. J.T.; 31. C.S.; 32. G.M.; 35. M.P.; 36. M.C.; 40. J.Z.
Pooled IgM	(1)–(19)	κ λ	1. R.K.; 10. M.P.; 15. M.E.; 19. E.F.; 29. J.W.
Bence-Jones proteins		κ	10. M.P.; 29. J.W.
Bence-Jones proteins		λ	29. J.W.

* Coats (1)–(19) are purified monoclonal IgM proteins from patients with Waldenström's macroglobulinaemia.

The titres and specificities of the anti-IgM antibodies in the twelve positive subjects are summarized in Table 4. By analogy with serum anti-IgA antibodies (Fudenberg & Vyas, 1971), an anti-IgM agglutinating all of the IgM protein coats is designated a 'class-specific anti-IgM' and an anti-IgM agglutinating one or a few of the IgM coats is designated 'anti-IgM of limited specificity'. Four of the twelve positive serum specimens contained class-specific anti-IgM (10. M.P.; 15. M.E.; 19. E.F.; 29. J.W.); the reason for the failure of 29. J.W. to react with IgM coats (11), (12) and (16)–(19) is unknown. Six subjects had anti-IgM of limited specificity reacting with only one IgM coat; four reacted with IgM (7) in titres from 1:4 to 1:32 (3. P.R.; 21. R.V.; 22. J.S.: 39. D.M.), one (36. M.C.) reacted with IgM (10), and one (31. C.S.) reacted with IgM (18). In five of these six sera, only the homologous positive coat was effective in inhibition experiments. However, the anti-IgM (7) antibodies in subject 39. D.M. were also inhibited by IgM (8) although a higher concentration was

required than with IgM (7) to achieve inhibition. Serum 30. J.T. contained anti-IgM with a limited specificity against a determinant shared by IgM (17) and IgM (18). A lack of serum precluded further studies with 30. J.T. and 39. D.M. Detailed studies with serum 1. R.K. demonstrated inhibition by normal human sera including 85·2% of 122 Caucasians, 26·1% of 23 Negroes and 27·7% of 155 Japanese; this anti-IgM defines an inherited allotypic marker on the μ chains of IgMs (7), (8), (10) and (11) which we designated Im μl (Wells, Bleumers & Fudenberg, 1972). Autologous IgG was isolated from the serum of 1. R.K., 3. P.R., and 21. R.V. and in each case confirmed the anti-IgM antibodies were IgG class. In the case of 1. R.K. and 3. P.R. autologous IgM did not inhibit the anti-IgM antibodies; the other ten

TABLE 4. Data on the titres and specificities of anti-IgM antibodies in the twelve positive subjects

Subject No.	IgM protein coat	Serum antibody titre	Inhibition by IgM protein solutions: IgM	Inhibition by IgM protein solutions: Limiting inhibitory concentration (μg/ml)
1. R.K.	(7)	256*	(7) & (11)	16
	(7)	256	(8) & (10)	64
	(11)	256	(7) & (11)	16
	(11)	256	(8) & (10)	64
	(8)	64	(7) & (11)	1
	(8)	64	(8) & (10)	8
	(10)	64	(7) & (11)	1
	(10)	64	(8) & (10)	4
3. P.R.	(7)	32	(7)	13
10. M.P.	(1)–(19)	16	Insufficient serum	
15. M.E.	(1)–(19)	4	Insufficient serum	
19. E.F.	(1)–(19)	8	Insufficient serum	
21. R.V.	(7)	32	(7)	26
22. J.S.	(7)	4	Insufficient serum	
29. J.W.	(1)–(10) (13)–(15)	8	Insufficient serum	
30. J.T.	(17) & (18)	8	(17 & (18)	8
31. C.S.	(18)	8	(18)	8
36. M.C.	(10)	4	Insufficient serum	
39. D.M.	(7)	32	(7)	15
			(8)	50

* Titres given as reciprocal of lowest dilution with agglutination.

positive sera were not tested with autologous IgM. The following proteins were all negative in inhibition experiments against specific anti-IgM antibodies: normal IgG, normal IgA, ruminant IgM (bovine or caprine), κ chains, and $\hat{\lambda}$ chains.

DISCUSSION

The incidence of anti-IgM antibodies in 30% of forty subjects with selective IgA deficiency contrasts with an earlier reported incidence of 4·2% of 378 normal subjects and subjects

having multiple blood transfusions or multiple pregnancies (Leikola *et al.*, 1971). There have been few detailed studies of anti-IgM antibodies and the underlying mechanisms involved in their development have not yet been characterized. They do not appear to be associated clinically with reactions to injected IgM comparable to the syndromes (including rapidly fatal anaphylactic reactions) which have been described between injected IgA and anti-IgA antibodies (Fudenberg *et al.*, 1968; Vyas & Fudenberg, 1970; Fudenberg & Vyas, 1971). The immediate origin of the anti-IgM was obvious in 36. M.C., a 3-yr-old girl with ataxia telangiectasia. Her two brothers had previously died with ataxia telangiectasia and lymphosarcoma and in an attempt to prevent a similar course she had been managed with regular infusions of plasma from her father over 3 yr (Ammann *et al.*, 1969). Analysis of stored pre- and post-infusion samples of her serum demonstrated anti-IgM (10) antibodies of 1:4 titre immediately postinfusion, with the anti-IgM (10) usually disappearing before the following infusion in 3–4 weeks. Anti-IgM (10) antibodies were present at a titre of 1:16 in her father. No reactions were observed during or after these plasma infusions with the anti-IgM (10). None of the other eleven positive subjects had a history of infusion of blood or plasma to account for their anti-IgM antibodies.

Several immunologic abnormalities have been reported in selective IgA deficiency including the presence of precipitating antibodies against ruminant proteins in 24–56% of such subjects, (Buckley & Dees, 1969; Ammann & Hong, 1971; Huntley *et al.*, 1971; Leikola & Vyas, 1971). These antibodies were of IgG class and were directed against determinants in the Fc portion of ruminant IgM proteins (Huntley *et al.*, 1971). We refer to the present antibodies as 'reverse rheumatoid factors' as they are directed against human IgM. Several points of evidence confirmed that the IgG antibodies against human IgM were a distinct species of antibody from those against ruminant IgM, e.g. individual serum specimens could be positive for one but negative for the other and ruminant proteins were not able to inhibit the present anti-IgM systems. There are other abnormalities involving IgM in selective IgA deficiency. As an apparent compensatory mechanism for the deficiency of IgA as the main secretory immunoglobulin, the level of IgM in intestinal secretions increases up to fifteen times the normal level with increased numbers of plasma cells synthesizing IgM (Stobo & Tomasi, 1967; Ammann & Hong, 1971; Brandtzaeg, 1971). Monomer IgM may be detected in both serum and secretions (Stobo & Tomasi, 1967). These abnormalities may permit the absorption of dietary components which secretory IgA would normally exclude and lead to the development of precipitating antibodies to these 'foreign' antigens (Huntley *et al.*, 1971). The development of precipitating antibodies to dietary constituents has been observed in children with coeliac disease but these subjects had high serum IgA and low serum IgM levels (Kenrick & Walker-Smith, 1970). It is difficult to visualize how the human IgM components could gain access to the lymphoid system and sensitize a subject developing anti-IgM antibodies except via the intestinal route; eleven of the twelve subjects with anti-IgM antibodies did not have a history of parenteral administration of blood derivatives.

Subjects with selective IgA deficiency exhibit a high incidence of auto-immune diseases and gastro-intestinal diseases; only seventeen of the present forty subjects were considered clinically normal but our population sample is undoubtedly biased. In a recent review, only three of thirty were considered normal after detailed investigation (Ammann & Hong, 1971). Nevertheless selective IgA deficiency is apparently a relatively mild immunologic deficiency since many subjects demonstrate normal survival. Long-term follow-up studies will be necessary to define the natural history of these antibodies and their biological significance.

Blood transfusion reactions have been clearly associated with anti-IgA antibodies (Fudenberg *et al.*, 1968), but similar reactions have, thus far, not been associated with anti-IgM antibodies (Leikola *et al.*, 1971). This may be related to the low titres of anti-IgM antibodies in such subjects who have been transfused and it is possible that high titre anti-IgM antibodies may be associated with transfusion reactions. Although anti-IgM antibodies appeared to be more frequent in individuals with recurrent infections, the difference was not statistically significant at the 5% level. At this stage, they represent yet another immunologic abnormality in subjects with selective IgA deficiency.

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