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Association of anti-IgA antibodies with adverse reactions to gamma globulin infusion

Rima Rachid, MD^{a,*}, Mariana Castells, MD, PhD^b, Charlotte Cunningham-Rundles, MD, PhD^c, and Francisco A. Bonilla, MD, PhD^a

^aChildren's Hospital Boston, Harvard Medical School, Division of Allergy and Immunology, Boston, MA, USA

^bBrigham and Women's Hospital, Harvard Medical School, Division of Allergy and Immunology, Boston, MA, USA

^cMount Sinai Medical Center, New York, NY, USA

Keywords

IgA deficiency; Anti-IgA antibodies; Anaphylaxis; Intravenous Immunoglobulin; Subcutaneous Immunoglobulin

Serum IgG anti-IgA antibody has been associated with the development of adverse reactions, (including non-IgE mediated anaphylaxis) to intravenous immunoglobulin (IVIG) in patients with undetectable IgA (here defined as <7 mg/dL).¹ Class-specific anti-IgA antibodies bind both IgA1 and IgA2; they are found in 25–30% of IgA-deficient individuals, but not in those with IgA > 7mg/dL.² Subclass-specific (or limited specificity) anti-IgA reacts with only one subclass [IgA1, IgA2m(1) or IgA2m(2)].² It is estimated that up to 40% of patients with selective IgA deficiency and 9–25% of patients with common variable immunodeficiency (CVID) may have IgG anti-IgA.³ IgE anti-IgA has been found much less frequently. Three of four patients with IgE anti-IgA had anaphylaxis to gammaglobulin or other blood products.^{4,5}

We conducted a retrospective and prospective observational study to evaluate the possible association with adverse reactions of IgG and/or IgE anti-IgA in IgA-deficient patients receiving IVIG or subcutaneous immunoglobulin (SCIG) at Children's Hospital Boston, Boston, MA, and Brigham and Women's Hospital, Boston, MA. All investigations were conducted according to the policies and procedures of the Institutional Review Boards of both institutions.

Among 425 immunodeficient patients receiving IgG therapy, we identified 35 (8.2%) with undetectable IgA; 22 were enrolled. Twenty of these were studied retrospectively (medical record review for one year prior to enrollment) and prospectively (6 months) for symptoms

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*Corresponding author: Children's Hospital, Immunology Division, Fegan 6, 300 Longwood Ave, Boston, MA 02115; phone: 617-355-6117; fax 617-730-0310; rima.rachid@childrens.harvard.edu.

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related to IgG infusion. Thirteen patients (11 CVID, 2 IGAD) were excluded due to increase in IgA level (3), lack of consent (7), or non-adherence with study procedure (3). Blood was collected at enrollment and after the 6 month observation period. Subjects #22 and #23 were only studied prospectively since they did not receive IgG in the year prior to obtaining the serum specimens. Data were collected with respect to the IgG product, lot number, dose, rate of infusion, use of premedications, and symptoms recorded within 1 hour after the end of the infusion (acute) or up to 72 hours later (delayed). Symptoms were graded as mild (treated by the patients or medical staff without discontinuing the infusion), moderate (requiring telephone contact with, or a visit to an outpatient setting for assistance from a health-care provider, or requiring cessation of the infusion), or severe (requiring an emergency room visit or hospitalization, or resuscitation).

We measured serum levels of IgA1, IgA2 and IgG anti-IgA1 and anti-IgA2 by ELISA using myeloma controls to establish approximate concentration standard curves. Serum specimens were also studied at the Mayo Clinic Laboratory (Rochester MN) using a Luminex®-based assay system and in the Red Cross Laboratory (Philadelphia, PA) by passive hemagglutination. IgE anti-IgA1 and anti-IgA2 were measured by ImmunoCAP assays at ViraCor-IBT Laboratories (Lenexa, KS).

In all patients throughout the study, only mild symptoms were reported, including headache, fatigue and malaise. These were of a nature and frequency commonly seen in many clinical trials of IgG therapy that routinely exclude IgA-deficient patients. Therefore no attempt was made to correlate these symptom data with results of immunoassays.

Results of the immunochemical analyses are shown in Table E1 (available online). Background levels for IgG anti-IgA1 or IgA2 ELISA ranged from 51–240 ng/mL (lower limit of assay detection, sera diluted 1:100). Three subjects had levels well above this range (504–4,528 ng/mL) (Table 1). Two individuals (#23 and #32) had class-specific IgG anti-IgA by ELISA. One subject (#33) had subclass-specific IgG anti-IgA2. Subjects #32 and #33 have only ever received SCIG and have never had adverse reactions. Their ability to tolerate IVIG is unknown. Seven years prior to enrollment, patient #23 had anaphylaxis requiring epinephrine during infusion of an IVIG product containing <10 mcg/mL IgA and ceased IgG therapy. The specimen for measurement of IgG anti-IgA was obtained at the time of enrollment in the prospective study, when she began receiving SCIG, which she has now tolerated for 2 ½ years without any adverse effects. She had a level of IgG anti-IgA (mean of anti-IgA1 and anti-IgA2) of 3,946 ng/mL. The Mayo lab reported a total IgG anti-IgA level >1,000 arbitrary units and in the Red Cross Laboratory IgG anti-IgA was detected. Her IgG anti-IgA level repeated 2 ½ years later at the Mayo Laboratory was still >1000 AU.

The two patients that had class-specific IgG anti-IgA in our assay also tested positive in the Mayo laboratory. The one individual with subclass-specific IgG anti-IgA2 did not test positive in the Mayo laboratory (result in the “equivocal” range). Subject #23 also tested positive in the Red Cross laboratory; subject #32 did not. The test was repeated with the same result. The reason for the discrepancy is unknown. The Red Cross laboratory did detect the subclass-specific IgG anti-IgA2 that was also found by our ELISA in pt. #33. Overall, there is good agreement between our results and these two clinical reference laboratories. IgE anti-IgA was not detected in any patient.

Anaphylaxis is very rare among patients receiving IVIG.⁶ Therefore, a possible increased risk associated with IgG anti-IgA remains very difficult to quantify. None of the patients evaluated developed a significant reaction during the study period. We could not address the potential clinical significance of the subclass-specific anti-IgA2 with respect to IVIG, since the only such patient we identified had only ever received SCIG.

Is IgG anti-IgA a “biomarker” of increased risk of non-IgE mediated anaphylaxis to gammaglobulin infusion containing IgA? Several anecdotal reports (including this one) suggest this may be the case. The mechanism whereby anti-IgA antibodies might cause an adverse reaction to IgG that contains some IgA is open to speculation. It has been reported that some individuals react to products with “high” IgA and tolerate products with “low” IgA.^{7, 8} This could be interpreted as an indication that the reaction mechanism involves interaction of IgG anti-IgA with infused IgA. However, patient #23 appears not to tolerate IVIG products containing even trace amounts of IgA and some patients with IgG anti-IgA tolerate IVIG without symptoms.⁹

Given the rarity of anaphylaxis to IVIG, much larger prospective studies are required to establish more clearly any possibility of increased risk associated with IgA deficiency. It is not clear that class or sub-class specific IgG anti-IgA antibodies have clinical relevance. Our data and others' suggest that further study of a possible association is warranted. In an individual patient, the presence of IgG anti-IgA may indicate a need for closer monitoring, or consideration of alternative therapy such as SCIG, which appears to be tolerated in many of these patients.

Capsule summary

In a cohort of 22 IgA-deficient patients receiving gammaglobulin, we found three with IgG anti-IgA antibodies, but only one had ever received intravenous infusion, and had non-IgE mediated anaphylaxis. All three tolerate subcutaneous IgG.

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Abbreviations

CVID	common variable immunodeficiency
IGAD	IgA deficiency
IMIG	intramuscular immunoglobulin
IVIG	intravenous immunoglobulin
SCIG	subcutaneous immunoglobulin

REFERENCES

1. Eijkhout HW, van den Broek PJ, van der Meer JW. Substitution therapy in immunodeficient patients with anti-IgA antibodies or severe adverse reactions to previous immunoglobulin therapy. *Neth J Med.* 2003; 61:213–7. [PubMed: 12948165]

2. Sandler SG, Eckrich R, Malamut D, Mallory D. Hemagglutination assays for the diagnosis and prevention of IgA anaphylactic transfusion reactions. *Blood*. 1994; 84:2031–5. [PubMed: 8081004]
3. de Albuquerque Campos R, Sato MN, da Silva Duarte AJ. IgG anti-IgA subclasses in common variable immunodeficiency and association with severe adverse reactions to intravenous immunoglobulin therapy. *J Clin Immunol*. 2000; 20:77–82. [PubMed: 10798611]
4. Ferreira A, Garcia Rodriguez MC, Fontan G. Follow-up of anti-IgA antibodies in primary immunodeficient patients treated with gamma-globulin. *Vox Sang*. 1989; 56:218–22. [PubMed: 2474899]
5. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. Detection of IgE antibodies to IgA. *N Engl J Med*. 1986; 314:560–4. [PubMed: 3945295]
6. Brennan VM, Salome-Bentley NJ, Chapel HM. Prospective audit of adverse reactions occurring in 459 primary antibody-deficient patients receiving intravenous immunoglobulin. *Clin Exp Immunol*. 2003; 133:247–51. [PubMed: 12869031]
7. Hedderich U, Kratzsch G, Stephen W, Dichtelmuller H, Olischlager K, Heimpel H. Immunoglobulin substitution therapy in a patient with primary hypogammaglobulinaemia and anti-IgA antibodies. *Clin Allergy*. 1986; 16:339–44. [PubMed: 3488850]
8. Cunningham-Rundles C, Wong S, Bjorkander J, Hanson LA. Use of an IgA-depleted intravenous immunoglobulin in a patient with an anti-IgA antibody. *Clin Immunol Immunopathol*. 1986; 38:141–9. [PubMed: 3079685]
9. Ferreira A, Garcia Rodriguez MC, Lopez-Trascasa M, Pascual Salcedo D, Fontan G. Anti-IgA antibodies in selective IgA deficiency and in primary immunodeficient patients treated with gamma-globulin. *Clin Immunol Immunopathol*. 1988; 47:199–207. [PubMed: 2450712]

Table 1

Characteristics of patients with positive anti-IgA antibodies.

Study #	Sex	Age ^a (years)	Dx., SC/IV ^b	Spec. No.	IgA1 (ng/mL)	IgA2 (ng/mL)	CHB IgG anti-IgA1 (ng/mL)	CHB IgG anti-IgA2 (ng/mL)	Mayo IgG anti-IgA (AU) ^c	RC IgG anti-IgA ^d
23	F	26	CVID, IV	1	52	20	4528	3363	>1000	Anti-IgA
32	F	60	CVID, SC	1	150	32	2821	1859	684	ND
33	M	60	CVID, SC	2	121	20	4398	3563	>1000	ND
				1	204	116	167	755	172	Anti-IgA2
				2	253	71	130	504	133	Anti-IgA2

^a Age when first serum specimen obtained

^b Therapy at time when serum specimen obtained, IV = intravenous infusion; SC = subcutaneous infusion;

^c AU = arbitrary units, <100 = negative, 100–200 = equivocal, >200 = positive; maximum result reported >1,000

^d Qualitative test, results reported as type of anti-IgA detected, or not detected (ND)

Table E1

Results of immunochemical analysis.

Study #	Sex	Age ^d (years)	Dx., SC/IV ^b	Spec. No.	IgA1 (ng/mL)	IgA2 (ng/mL)	CHB IgG anti-IgA1 (ng/mL)	CHB IgG anti-IgA2 (ng/mL)	Mayo IgG anti-IgA (AU) ^c	RC IgG anti-IgA ^d
01	F	8	CID, IV	1	983	1261	127	170	91	ND
02	F	43	CVID, IV	2	824	344	98	164	67	ND
03	F	43	CVID, IV	2	1030	632	60	63	24	ND
04	F	31	CVID, SC	2	445	275	63	68	33	ND
06	F	40	IGAD, IV	2	436	220	138	126	84	ND
07	F	37	CVID, IV	2	375	297	170	128	63	ND
08	F	17	CVID, IV	2	185	96	103	92	53	ND
13	F	15	G4/IGAD, IV	2	550	286	129	135	67	ND
14	M	13	Hypogam, IV	2	327	305	126	155	56	ND
15	M	35	CVID, IV	2	318	287	68	93	45	ND
18	M	17	CVID, IV	2	263	159	241	232	114	ND
19	M	6	Hypogam, IV	2	469	330	67	93	35	ND
20	F	23	CVID, IV	2	459	165	78	96	48	ND
21	F	55	CVID, IV	2	380	150	97	164	36	ND
22	M	6	Hypogam, IV	2	342	418	124	108	52	ND
					343	175	145	174	73	ND
					661	232	59	58	22	ND
					393	109	71	81	45	ND
					245	82	87	89	41	ND
					238	75	91	100	25	ND
					2473	621	118	65		ND
					1166	764	82	106		ND
					236	110	80	93	68	ND
					225	114	60	73	57	ND
					185	59	49	58	14	ND
					190	53	74	75	26	ND
					222	89				ND

Study #	Sex	Age ^d (years)	Dx., SC/IV ^b	Spec. No.	IgA1 (ng/mL)	IgA2 (ng/mL)	CHB IgG anti-IgA1 (ng/mL)	CHB IgG anti-IgA2 (ng/mL)	Mayo IgG anti-IgA (AU) ^c	RC IgG anti-IgA ^d
23	F	26	CVID, IV	1	52	20	4528	3363	>1000	Anti-IgA
30	F	53	CVID, SC	1	1017	323	115	109	82	ND
31	M	55	CVID, IV	2	773	337	125	115	75	ND
32	F	60	CVID, SC	2	95	4	97	75	54	ND
33	M	60	CVID, SC	2	58	0	75	70	46	ND
34	F	80	CVID, IV	2	150	32	2821	1859	684	ND
35	F	29	Hypogam, SC	2	121	20	4398	3563	>1000	ND
				1	204	116	167	755	172	Anti-IgA2
				2	253	71	130	504	133	Anti-IgA2
				1	130	64	51	98	80	ND
				2	127	47	91	94	77	ND
				1	124	84	79	81	65	ND
				2	120	92	63	52	55	ND

An empty cell indicates the test was not done.

^a Age when first serum specimen obtained

^b G2=IgG2 deficiency, G4=IgG4 deficiency, CID=combined immunodeficiency (see list for other abbreviations); hypogam=unspecified hypogammaglobulinemia, consisting of low total IgG level with apparent adequate vaccine antibodies; therapy at time when serum specimen obtained, IV = intravenous infusion; SC = subcutaneous infusion;

^c AU = arbitrary units, <100 = negative, 100-200 = equivocal, >200 = positive; maximum result reported >1,000

^d Qualitative test, results reported as type of anti-IgA detected, or not detected (ND)