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REVIEW

Anaphylaxis to IVIG

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Abstract Anaphylactic reactions are a known complication in some IgA-deficient patients receiving blood or plasma transfusions. It is of particular interest that anaphylaxis has been observed in patients with common variable immunodeficiency (CVID) who are receiving intravenous gammaglobulin (IVIG), and in that, although these patients have an impaired response to common vaccines, they retain the ability to produce autoantibodies. In this study, we review IgA antibodies (both IgG- and IgE-mediated reactions) in patients with CVID and hypogammaglobulinemia, anaphylaxis in antibody immunodeficient patients receiving IVIG, and proposed mechanisms of desensitization and prevention of anaphylactic reactions in immunodeficient patients receiving IVIG. We summarize and assess the 23 case reports documented in the literature that have described anaphylactic reactions in immunodeficient patients receiving IVIG since 1962 until currently, and make a comparison of their immunoglobulin levels, IgG anti-IgA, IgE anti-IgA, concentration of IVIG, IgA content in IVIG, method used to detect antibodies, length of treatment, and any subsequent tolerated treatment documented.

Keywords Anaphylaxis · Anaphylactic · IVIG · CVID · Autoantibodies · IgA · IgE · IgG

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Introduction and Historical Aspect

The first administration of intravenous gammaglobulin (IVIG) was by Edwin J. Cohn (Cohn 1945). Anaphylactic reactions in selective IgA-deficient patients were first linked to anti-IgA antibodies in 1962 (Gallagher and Buckley 1962). Patients with common variable immunodeficiency (CVID) retain the ability to produce autoantibodies. High titers of antibodies to IgA are found in these patients, even though they make no or impaired response to common vaccines (Barandun et al. 1962; Gallagher and Buckley 1962).

It has been observed that these anaphylactic reactions are found in patients who have hypogammaglobulinemia secondary to deficient synthesis of gammaglobulins, rather than in patients who lose gammaglobulins through the kidney or the gut. Early laboratory studies have not demonstrated that histamine or serotonins have a role in the development of this allergic phenomenon, and treatment with histamine and serotonin antagonists did not alleviate the anaphylactic reactions (Barandun et al. 1962).

Barandun, however, did observe a decrease in the level of all components of the complement system following IVIG in all patients regardless of reaction, and even more pronounced in those with anaphylaxis. This decrease is possibly due to either a complement-fixing antigen–antibody reaction or a consumption of complement by the gammaglobulin treatment (Barandun et al. 1962). Hedderich et al. (1986) also described anaphylactic reactions that correlated with decreased C3:albumin and C4:albumin ratios right after IVIG, supporting earlier hypotheses that complement are consumed following gammaglobulin treatment.

A kinin derivative from C2 may also be the mediator of these antigen–antibody complexes activated by kallikrein (Klemperer et al. 1968). It was also noted that small

amounts of IgG dimers and polymers were found in the IVIG, and that these IgG aggregates are the trigger of these reactions in agammaglobulinemic patients (Barandun et al. 1962; Marcus 1960).

Anaphylaxis/Anaphylactic Reaction in IgA Deficiency (Blood/Plasma)

Significant allergic reactions triggered by blood and plasma products are a well-known phenomenon (Vamvakas and Pineda 2001). The mechanisms for this include: antigens in the blood transfusion to which the donor had already been presensitized to, biologically active mediators infused that were formed during storage of the blood, donor IgE antibodies against some antigens in the recipient's blood being transferred to the recipient, and recipients with preformed antibodies to IgA being exposed to transfused IgA (Vassallo 2004). The preformed antibodies can be class-specific or subclass-specific, with the most severe reactions occurring in IgA-deficient patients with class-specific IgG anti-IgA antibodies. In contrast, patients with low or normal IgA levels with preformed subclass antibodies are at risk of minor allergic reactions (Sandler et al. 1995).

In one study, the prevalence of selective IgA deficiency was 1 in 328 blood donors in the United States, defined by immunodiffusion assay of IgA concentrations below 5 mg/dL (Pereira et al. 1997). Sandler et al. (1994) found that 1 of 1200 Americans has coexisting IgA deficiency and anti-IgA antibodies. In his study to prevent IgA-related anaphylactic transfusion reactions, Sandler found that 18 % of 359 patients' sera showed anti-IgA antibodies of any class in the setting of anaphylactic to anaphylaxis transfusion reactions, suggesting that more often anaphylaxis/anaphylactic reactions are not due to IgG anti-IgA antibodies (Sandler et al. 1994). Incidence reported in the literature of severe allergic reactions secondary to transfusions includes: 4.3 of 100,000 red blood cell (RBC) transfusions and 62.6 of 100,000 platelets transfusions in Quebec (Kleinman et al. 2003); and 10.4 of 100,000 platelet transfusions, 3.5 of 100,000 plasma transfusions, and 1.7 of 100,000 RBC transfusions were reported in Cleveland Clinic's retrospective review (Domen and Hoeltge 2003). Incidence of IgA-related severe allergic reactions to blood transfusions was found to be 1.7 of 100,000 and 2.1 of 100,000 in two studies (Bjerrum and Jersild 1971; Pineda and Taswell 1975). This can be summarized into approximately 1 in 50,000 incidence of IgA-related major transfusion reactions from whole blood or packed cells. Given that severe allergic reactions to blood transfusions occur in just 2.4 % of those with IgA deficiency and coexisting anti-IgA antibodies, there is clearly variability in the pathogenesis of anti-IgA antibodies (Sandler et al. 1994).

IgA Antibodies in CVID and Hypogammaglobulinemia

In the Western world, selective IgA deficiency is the most common primary immunodeficiency, and up to 20 % of IgA-deficient patients have an associated IgG subclass deficiency, most often IgG2 with or without IgG4 deficiency (Oxelius et al. 1981).

Björkander et al. (1987) studied 85 patients with CVID and thirty-nine patients with hypogammaglobulinemia, classifying them into different categories, and found that the highest frequency of anti-IgA antibodies occurs in patients with combined IgA–IgG2 deficiency, occurring 60 % of the time. Overall, they found antibodies against IgA in 29 % of IgA-deficient patients. They also found that IgG anti-IgA antibodies were most often of the IgG1 subclass, but did also occur with IgG2, IgG3, and IgG4 subclasses. Occasionally, they observed IgD anti-IgA and IgM anti-IgA antibodies (Björkander et al. 1987).

Human antibodies to human IgA can be detected by sensitive enzyme-linked immunosorbent assay (ELISA), passive hemagglutination, or laser nephelometry. Passive hemagglutination uses purified IgA myeloma proteins coating indicator red blood cells with the coupling agent of chromium chloride. It is presumed that these anti-IgA antibodies are produced after exposure or immunization with IgA containing globulin (Vyas et al. 1968).

Among the different diagnostic tests for anti-IgA antibodies, passive hemagglutination and flow cytometry are reliable but technically challenging, while the immunoassays are less reliable due to a lower sensitivity (Vassallo 2004). There is a new test for the detection of IgA deficiency and detection of antibodies to IgA using the particle gel immunoassay method which has been shown to be rapid and reliable. IgA molecules are coated with red high-density polystyrene beads, and when these beads agglutinate, it is considered a positive reaction (Salama et al. 2001). This method of detection was used in emergency diagnosis of all anaphylactic reaction transfusion reactions as well as in IgA-deficient patients to test for antibody status. Although it does not quantify IgA antibodies' level, it has been shown to be a simple and reliable way of diagnosing anaphylaxis due to anti-IgA antibodies in an emergent setting (Oltean et al. 2014).

Anaphylaxis/Anaphylactic Reactions in Antibody Immunodeficiency Diseases

While the mechanism of IgE anti-IgA antibodies is classified as a Type I hypersensitivity anaphylaxis reaction, there is a hypothesis that an alternative mechanism exists mediated by IgG and basophils with mast cell

degranulation causing anaphylactic reactions from these preparations. This latter pathway is associated with an increase in C3a, C4a, and C5a as the anaphylatoxins. Tryptase levels are not elevated in the IgG-mediated pathway. The decrease or loss of anti-IgA antibody activity in these cases was found to be associated with a decrease in complement components (Kiani-Alikhan et al. 2010).

Several investigators (Hedderich et al. 1986; Horn et al. 2007) have observed nodular lymphoid hyperplasia in patients who developed anaphylactic reactions to IVIG. Horn et al. (2007) observed that seven of eight patients displayed lymphoproliferation, with five patients having nodular lymphoid hyperplasia and anti-IgA antibodies, suggesting a possible association between IVIG anaphylactic reactions, nodular lymphoid hyperplasia, and anti-IgA antibodies.

IgG Anti-IgA-Mediated Reactions: The Presence of Antibodies in the General Population and in Primary Antibody Deficiencies

In healthy individuals who have selective IgA deficiency, antibodies were found in 37 % of patients with IgA levels below 5 mg/dL (Petty et al. 1979) and 29 % in those with levels under 0.05 mg/dL (Björkander et al. 1987). Antibodies were found in 60 % of those who had both IgA deficiency and IgG2 deficiency (Björkander et al. 1987). For patients with IgA deficiency whose course was complicated an autoimmune disorder, antibodies were found in 50 % with rheumatoid arthritis, 77 % in juvenile rheumatoid arthritis, and in all patients with systemic lupus erythematous (Petty et al. 1979).

Hedderich et al. (1986) supported that the severity of reactions was linked to IgA content of the gammaglobulin treatment as well as infusion rate. They found a biphasic nature of the IgG anti-IgA antibodies, with an initial increase and subsequent decrease in the IgA1 isotype, during which administering IVIG again resulted in desensitization (Hedderich et al. 1986).

Cunningham-Rundles et al. (1993) reported an anaphylactic reaction following the fourth infusion of IVIG in a patient with CVID, who initially was treated with intramuscular immunoglobulin and later with IVIG. This was associated with activation of complement system as demonstrated by increased C3a and C4a levels. This finding was not directly linked to the patient's development of anaphylactic shock. Complement activation is thought to be possibly due to the formation of IgG anti-IgA complexes (Cunningham-Rundles et al. 1993).

Sundin et al. (1998) found from in vitro experiments that when a small amount of IgA was added, all of it was still bound by IgG anti-IgA antibodies, forming both IgG–IgA dimers and polymers. Although this formed large aggregates with occupied binding sites, the IgA was still recognized on ELISA because of a small enough IgA antigen, such that favorable competition was permitted. This was not found to be true when the serum level of IgA was increased, as this caused the IgA antigen to competitively inhibit any anti-IgA activity, by decreasing the quantity of available monomeric IgA (Sundin et al. 1998).

de Albuquerque Campos was not able to demonstrate a consistent association between the detection of IgG anti-IgA antibodies during anaphylactic reactions to IVIG. They also looked at the different IgG subclasses, given their different roles in fixing complement, and found no correlation between the IgG anti-IgA subclass types with anaphylactic reactions. They did note that IgG1 anti-IgA was the most predominant subclass found in 25 % of their patients' sera, followed by IgG2 and IgG4 (de Albuquerque et al. 2000).

In another study, IgG anti-IgA antibodies were only found in CVID patients with associated IgA deficiency. All eight of their patients who had IgG anti-IgA antibodies lacked circulating IgA^+ switched memory B cells, suggesting this as a prerequisite to development of IgG anti-IgA antibodies (Horn et al. 2007).

Horn et al. (2007) found a commonality between three patients who developed anaphylactic symptoms to IVIG treatment that all were IgA deficient and their IgA^+ B cells were of the CVID type II classification (defined as $CD27^+$ IgM^- IgD^- memory B cells with >0.4 % of peripheral blood mononuclear cells). This suggests that clinicians may test patients with IgA deficiency and IgA^+ B cells for IgG anti-IgA if they are of the CVID type II classification and require IVIG, but this would require more research prior to validation (Horn et al. 2007).

IgE Anti-IgA-Mediated Reaction in Hypogammaglobulinemia/CVID

Burks was the first to identify IgE anti-IgA antibodies via ELISA in two patients with CVID with associated IgA deficiency that had experienced several episodes of anaphylaxis to IVIG. The first patient had increasing levels of IgE anti-IgA antibodies in the months prior to his anaphylactic reaction to IVIG. The second patient also had a correlation, and later showed undetectable levels of IgE anti-IgA antibodies during periods of tolerating the IVIG (Burks et al. 1986).

In Bjorkander's study (Björkander et al. 1987), IgE anti-IgA antibodies were not found in patients when they tested by indirect agglutination using alkaline phosphatase-conjugated goat anti-rabbit antibodies and sheep anti-rabbit antibodies as reagents. However, one of their patients who

developed anaphylactic shock to IVIG was found to have IgE anti-IgA antibodies when measured using an avidin–biotin step. It is a well-known recommendation to use immunoglobulin preparations low in IgA to prevent the observed immunization and adverse reactions to subsequent administrations (Björkander et al. 1987).

While Ferreira et al. (1988) found that the highest frequency of anti-IgA antibodies was found in patients with concomitant IgA and IgG2 subclass deficiency, they did find one exception of IgM anti-IgA antibodies and one with IgE anti-IgA1 antibodies in a patient who developed anaphylactic reaction to IVIG administration. In this patient, both titers to IgG anti-IgA1 and IgE anti-IgA1 antibodies disappeared after the treatment was stopped, with a lower IgE anti-IgA1 titer compared to one year prior. This was thought to be due to IgE consumption during the anaphylaxis. They used a very specific ELISA method to detect IgE anti-IgA antibody, with biotin–streptavidin using mouse mono-clonal anti-human IgE, biotinylated goat anti-human IgE, and horseradish peroxidase streptavidin conjugate (Ferreira et al. 1988).

Proposed Mechanisms of Desensitization and Prevention of Anaphylactic Reactions

A desensitization effect is seen in non-compatible IVIG. Barandun et al. (1962) described that 8–9 S gammaglobulin exposed to a pH of 4 at 37 °C has high affinity for tissues without anti-complement activity compared with the untreated standard gammaglobulin, and found a direct correlation of protective desensitization lasting as long as tissue receptors are saturated with the gammaglobulins. This was supported in one patient by an initial positive Coombs test, after which they converted into negative Coombs upon receiving IVIG (Barandun et al. 1962).

Barandun and Isliker (1986) found that, as a rule, after violent anaphylactic reactions to IVIG in antibody-deficient patients, there was a refractory period of tolerance to subsequent infusions, during which the initially sensitive patient can tolerate IVIG in large quantities for a period of up to 5 days after. They observed desensitization after a small dose of 1.5–3 g was administered. Patients were afterward able to tolerate larger amounts at faster infusion rates without eliciting the same life-threatening effects (Barandun and Isliker 1986).

Hedderich et al. (1986) observed that there is a biphasic nature of anti-IgA antibodies during treatment period, such that there is initially an increase followed by a decrease to lower levels than were present prior to treatment with IVIG, suggesting desensitization correlated with repeated exposure to the antigen.

Sundin et al. (1998) have observed the possibility of long-term tolerance induction and decreased levels of anti-IgA activity after long-term IVIG. One theory for this is induction of tolerance or anergy, such that anti-idiotypic antibodies from the infusion interact with autoantibodies of the patient and form complexes, which are cross-linked on surface immunoglobulin and Fc-receptors on B cells. A second theory is that during slow infusion IVIG and, thereby, IgG production (along with anti-IgA), there is continual supplementation of low levels of IgA and the complexes formed are subcutaneously deposited then slowly resorbed and rapidly cleared into circulation. It is hypothesized that the eradication of IgA activity in patients is due to anti-IgA antibodies being blocked by the IgA molecules from the infusion. The in vivo complexes observed between IgA and anti-IgA demonstrated that anti-IgA is diminished after treatment with IgA containing IVIG. The elimination of anti-IgA is most probably due to in vivo IgA complexes with anti-IgA which completely diminish the activity of anti-IgA without rebound (Sundin et al. 1998).

Salama et al. (2004) proposed an interesting strategy of preventing IgA anaphylaxis by pretreating the IVIG with the patient's autologous plasma in an ex vivo setting, which caused compatibility subsequently. Theoretically, this is plausible only if there are enough antibodies in the patient's plasma to significantly block causative immunogens. The case presented required 400 mL of plasma and 10 g of IVIG for complete or significant blockade of IgA molecules (Salama et al. 2004).

Ahrens et al. (2008) described a strategy to induce immune tolerance in patients who had a history of anaphylactic reactions from IVIG. Anti-IgA was initially detectable in all the patients, and after re-exposure of IVIG, anti-IgA was abolished, resulting in complete tolerance to IVIG in patients who once had anaphylactic reactions. The first patient received pretreated IVIG with autologous plasma, and anti-IgA diminished during treatment with tolerance of subsequent IVIG. The next three patients were documented to develop reactions after IVIG treatment that correlated with detectable levels of anti-IgA, but reactions never occurred during actual IVIG treatment. A second patient was given 10 g of IgA-depleted IVIG infused over 8 h, with subsequent undetectable levels of anti-IgA. This patient then tolerated 10 g of IVIG infused in 1 h as in standard conditions. Patients with lower levels of anti-IgA appear to develop tolerance more readily than those with high anti-IgA titers. This likely explains why the infusion speed has an impact. The conclusions of this study were that IgA anaphylaxis is correlated with IgA concentrated of IVIG, anti-IgA activity, infusion speed, and the time interval between treatments (Ahrens et al. 2008).

Kiani-Alikhan et al. (2010) also observed that in CVID patients with associated IgA-deficiency and a history of anaphylactic reactions to IgA containing IVIG whom later on received IVIG again at a slow rate of 10 g over 8 h showed tolerance and clearance of any circulating anti-IgA antibodies.

An in vivo murine model study demonstrated that anaphylaxis could be prevented. The first pathway is through the mouse IgG blocking the antigen before the antigen could induce the mast cells or basophils, thereby preventing activation and degranulation. The second pathway is through the inter-linking of inhibitory receptors on FcRIIb to the activating receptors FcRI on target cells (Strait et al. 2006). It has been suggested that expression of a mutation of novel gain-of-function splice variant of the FcRIIa receptor in patients with CVID is involved in increased pro-inflammatory signaling toward IgG, which then provokes recurrent anaphylactic reactions to IVIG (van der Heijden et al. 2013).

Another mechanism of desensitization was described by both de Albuquerque et al. (2000) and Eijkhout et al. (2003) through first administering subcutaneous immunoglobulin treatment on days 1–4 to the patient, and subsequently infusing IVIG on days 5–7, resulting in disappearance of anti-IgA antibodies and no anaphylactic reactions. This desensitization was found even with subcutaneous immunoglobulin that contained detectable amounts of IgA. Today subcutaneous immunoglobulin is the best way to overcome a previous reaction to IVIG.

Conclusion

The two pathways reviewed here focus on IgG anti-IgA versus IgE anti-IgA antibodies as causing anaphylactic or anaphylaxis type reactions. Type I hypersensitivity anaphylaxis reaction is via the IgE anti-IgA antibodies, whereas IgG anti-IgA is via IgG and basophils causing mast cell degranulation leading to anaphylactic reactions from these preparations. The IgG anti-IgA antibody pathway is responsible for the increases in C3a, C4a, and C5a as the anaphylatoxins. This finding is also supported by the loss of anti-IgA antibody activity correlating with a decrease in complement components (Kiani-Alikhan et al. 2010).

We have reviewed the literature of all patients with hypogammaglobulinemia or CVID who were reported to have anaphylactic or anaphylaxis type reactions to IVIG. In total, we found 23 patients that were documented, dating back to 1962 (Table 1). Many factors were analyzed for association or influence, including the patient's age, gender, indication for use of IVIG, baseline level of immunoglobulins with special attention to IgA, the concentration of IVIG used, the content of IgA in the IVIG treatment, the levels of IgG anti-IgA antibodies, the levels of IgE anti-IgA antibodies, the methods used to detect these antibodies, the length of treatment prior to developing a reaction, the symptoms/reactions reported, any measured post-treatment labs, and any subsequent tolerated immunoglobulin therapy (Table 1) (Barandun et al. 1962; Björkander et al. 1987; Burks et al. 1986; Cunningham-Rundles et al. 1993; de Albuquerque et al. 2000; Eijkhout et al. 2003; Ferreira et al. 1988; Gallagher and Buckley 1962; Hedderich et al. 1986; Horn et al. 2007; Rachid et al. 2011; Salama et al. 2004).

There is variability over time noted in some studies, such that titers of antibodies, whether IgG or IgE, were observed to be elevated prior to a reaction and subsequently decrease after the resolution of the anaphylactic episode and continuation of IVIG therapy. It is a well-known recommendation to use immunoglobulin preparations low in IgA to prevent the observed immunization and adverse reactions to subsequent administrations (Björkander et al. 1987). It is noted that the lower the IgA content in IVIG, the more likely a patient will tolerate IVIG therapy as there are not enough immune complexes to elicit a violent reaction.

Interestingly, correlations have been linked between anaphylactic symptoms to IVIG and patients of the CVID type II subtype, defined by $CD27^+$ IgM^- IgD^- memory B cells >0.4 % of peripheral blood mononuclear cells. One interesting recommendation is for clinicians to consider checking IgG anti-IgA antibodies in patients who are IgA deficient and have IgA^+ B cells, i.e., classified as the CVID type II, whom require IVIG therapy (Horn et al. 2007).

The method of detection is crucial, and IgE anti-IgA antibodies have been identified via ELISA and biotin–streptavidin step, although this more often the exception than the rule in anaphylaxis. In our literature review, there were some patients who had anaphylactic/anaphylaxis type reactions to IVIG and had anti-IgA antibodies, but more often than not patients have these antibodies and tolerate IVIG. The role of IgG or IgE anti-IgA antibodies needs more large-center studies, and recommendations to test patients for these antibodies cannot be made based on the available data. Likewise, IVIG should not be withheld from IgA-deficient patients as there is insufficient evidence to support this.

Multiple methods of desensitization for patients who have had anaphylactic or anaphylaxis type reactions are possible and have been described in the literature. These include subsequent infusions, desensitizing with subcutaneous immunoglobulin on days prior to IVIG, or by pretreating the IVIG with patient's autologous plasma. In conclusion, it is best to use IVIG with low IgA and IgG–IgA dimers content and subcutaneous immunoglobulin in at-risk patients.

Table 1 Literature review of patients with anaphylaxis and anaphylactoid reactions to IVIG

	Age	Indication	Patient IgA mg/dL	Patient IgG mg/dL	Patient IgM mg/dL	Patient IgG anti-IgA	Patient IgE anti-IgA	[gamma-globulin]
1	UK	CVID	0	280	14	1:640 **A**		
2	UK	CVID	0	46	0	1:8000		
3	40♂	Agammaglobulinemia						100 mL of 1.45 %, 10–15 drops/min
4	55♀	Hypogammaglobulinemia						100 mL of 1.45 %, 10–15 drops/min
5	14♂	Hypogammaglobulinemia						100 mL of 1.45 %, 10–15 drops/min
6	66♂	Hypogammaglobulinemia						100 mL of 1.45 %, 10–15 drops/min
7	15♂	CVID	0	280	0	1:8000	5–40 μg/mL by ELISA preceding anaphylactic reaction	
8	14♀	CVID	0	280	14	1:640	5 μg/mL by ELISA preceding anaphylactic reaction	
9	40♂	Hypogammaglobulinemia				Ranges of IgG anti-IgA_1 and IgA_2 from 1:2560 to 1:10240		pH-4 treated IVIG
10	♂	CVID						
11	24♀	CVID	1.2	0	0	IgG anti-IgA_1 1:12.800 IgG anti-IgA_2 1:3.200	0.7 μg/mL	
12	46♂	CVID	<1	554, with IgG_2 subclass deficiency	28	1:500		5 %
13	27♀	CVID	<1	210, with IgG_2 and IgG_3 subclass deficiency	21	1:200		5 %
14	♀	CVID				1:3200 IgG anti-IgA antibodies of all 4 subclasses	0	
15	♂	CVID	<0.1					6 %
16	♀	CVID	<0.1					6 %
17	♀	CVID	<0.1			Circulating anti-IgA antibodies found		6 %
18	40♂	CVID	<6.7 mg/dL	70.3	18.6	1:32		
19	49♀	CVID Type II (retained class-switched $CD27^+$ IgM^- IgD^-, >0.4 % of peripheral blood mononuclear cells	<0.06 g/L by nephelometry <0.0009 g/L by ELISA	1.74 g/L	0.24 g/L	1:400		
20	33♀	CVID Type II	<0.06 g/L by nephelometry <0.0009 g/L by ELISA	2.7 g/L	0.19 g/L	1:1600		
21	28♂	CVID Type I, <0.4 % of peripheral blood mononuclear cells	<0.06 g/L by nephelometry <0.0009 g/L by ELISA	<1.5 g/L	<0.2 g/L	1:6400		
22	33♀	CVID Type II	<0.06 g/L by nephelometry <0.0009 g/L by ELISA	3.21 g/L	0.22 g/L	1:6400		
23	26♀	CVID	IgA_1 = 52 μg/mL IgA_2 = 20 μg/mL			IgG anti-IgA_1 = 4528 μg/mL IgG anti-IgA_2 = 3363 μg/mL		

Table 1 continued

	IVIG IgA content	Method to detect antibodies	Preparation	Treatment length	AE	Post-treatment labs	Next tolerated treatment	References
1	0	Hemagglutination			Anaphylactic reaction	IgA by DARIA: <28 ng/mL to 6000 ng/mL	IVIG	Gallagher and Buckley (1962)
2	0	Hemagglutination			Anaphylactic reaction	IgA by DARIA: <28 ng/mL to 6000 ng/mL	IVIG	Gallagher and Buckley (1962)
3				90 min	Anaphylactic shock **B**		Gammavenin **C** and 45 g IVIG and pH4 IVIG **D**	Barandun et al. (1962)
4				90 min	Anaphylactic shock **B**		Gammavenin **C** and 45 g IVIG	Barandun et al. (1962)
5				90 min	Anaphylactic shock **B**		Gammavenin **C** and 45 g IVIG	Barandun et al. (1962)
6								Barandun et al. (1962)
7	15 µg/mL (Gammonativ)	Hemagglutination	Ion-exchange chromatography	20 mL	Anaphylactic reaction		Gammagard 1.6 µg/mL	Burks et al. (1986)
8		Hemagglutination		Seconds	Dyspnea, abdominal pain, cyanotic, vomit, defecation		Gammonativ 15 µg/mL	Burks et al. (1986)
9		Passive hemagglutination assay		90 min	Bronchospasm, shock	C3/albumin ratio and C4/album ratio both decreased after treatment		Hedderich et al. (1986)
10	<4 mg/L	Biotin-avidin enzyme immunoassay						Björkander et al. (1987)
11	0.02 and 0.07 mg/mL	Laser nephelometry for serum Ig ELISA for IgG subclasses IgE anti-IgA: Biotin-streptavidin enzyme immunoassay			Circulatory collapse, dyspnea	9 months later titers of IgG and IgE to IgA disappeared after treatment withdrawal		Ferreira et al. (1988)
12	0.6–1.1 µg/mL	ELISA			Hypotension, cyanosis, rigors, myalgias, sense of "impending doom"	Increased C3a and C4a levels		Cunningham-Rundles et al. (1993)
13	0.4–2.9 µg/mL	ELISA			Hypotension, myalgias, shortness of breath	Increased C3a and C4a levels		Cunningham-Rundles et al. (1993)
14	54 mg/dL	Biotin-avidin enzyme immunoassay			Malaise, shortness of breath, chest tightness			de Albuquerque et al. (2000)
15		Passive hemagglutination			Within 6 h anaphylactoid reaction			Eijkhout et al. (2003)
16		Passive hemagglutination			Within 6 h anaphylactoid reaction			Eijkhout et al. (2003)
17					Within 6 h anaphylactoid reaction			Eijkhout et al. (2003)
18	<0.1 mg/mL	Particle agglutination test			After 2–3 mL, pruritis, urticarial, vomiting, and respiratory distress	IgG anti-IgA titer 1:8		Salama et al. (2004)
19	<0.1 mg/mL (Octagam, Sandoglobulin)				Acute dyspnea, hypotension, generalized flush	3.7 % IgD^- $CD27^+$ cells, 0 % plasmablasts		Horn et al. (2007)
20	2.5 mg/mL (Intraglobin)				General edema, acute dyspnea, hypotension, cyanosis, unconsciousness	4.5 % IgD^- $CD27^+$ cells, 0 % plasmablasts IgG anti-IgA titer 1:1600		Horn et al. (2007)

Table 1 continued

	IVIG IgA content	Method to detect antibodies	Preparation	Treatment length	AE	Post-treatment labs	Next tolerated treatment	References
21	<0.1 mg/mL (Octagam)				Anaphylactoid reaction with capillary leak syndrome, acute renal failure, and pulmonary edema	1.2 % IgD^- $CD27^+$ cells, 0 % plasmablasts		Horn et al. (2007)
22	<0.1 mg/mL (Octagam)				Anaphylactoid reaction, exanthema rash, edema of upper and lower respiratory tract	2 % IgD^- $CD27^+$ cells, 0 % plasmablasts IgG anti-IgA titer 1:1600		Horn et al. (2007)
23	<10 μg/mL	ELISA			Non-IgE mediated anaphylaxis			Rachid et al. (2011)

A: Also had subclass specific antibodies; **B**: sudden onset dyspnea, circulatory collapse, mental status change, nausea, vomiting, chills, febrile, lumbar pain; **C**: 2.5 % IVIG degraded with proteolytic enzyme, 90 min; **D**: 1.5 % IVIG treated in pH 4 to remove anti-complement activity

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