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Brief Report

Selective IgA Deficiency and Blood Component Transfusion: In Search of the Lost Evidence

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Abstract: Background: Selective IgA deficiency (IgA-D) has been historically considered a high-risk entity for developing allergic/anaphylactic reactions after blood transfusion (AATRs). However, it has been suggested that the IgA-D-related anaphylactic transfusion reaction is not evidence-based. **Methods**: We conducted three different approaches to collect evidence about epidemiology, AATRs, and transfusion management of patients with IgA-D at La Fe University Hospital. Firstly, we analysed the prevalence of IgA-D in a population of patients diagnosed with acute leukaemia, The second approach consisted of collecting transfusion data from IgA-D patients. Finally, we reviewed the IgA levels of patients recorded in the hemovigilance system suffering an AATR. **Results**: IgA-D prevalence was 1 in 334 patients. At least one blood component was transfused to 23 patients diagnosed with IgA-D. Plasma was transfused to eight IgA-D patients, while six patients received red blood cells, platelets, and plasma. No adverse reactions were reported in any patient. AATRs occurred in 325 men and 264 women with a median age of 52 years. Severe reactions occurred in 56 patients (1/14,520 components). Mean IgA levels were 215 mg/dL (4–5570) for mild reactions and 214 mg/dL (14–824) for severe reactions (p = ns). Washed platelets were administered to two patients who developed severe and repeated AATRs. Both had normal IgA levels. **Conclusions**: Since the AATRs related to IgA-D are extremely low, as reported in current hemovigilance systems, IgA-D should not be considered a high-risk entity to develop AATRs. On the contrary, our findings support standard transfusion management of IgA-D patients.

Keywords: IgA deficiency; anaphylactic transfusion reaction; adverse transfusion reaction

Citation: Solves, P.; Bataller, A.; Gálvez, A.B.; Asensi Cantó, P.; Santiago, M.; Moreno, M.J.; Gómez-Seguí, I.; de la Rubia, J. Selective IgA Deficiency and Blood Component Transfusion: In Search of the Lost Evidence. *Hemato* **2024**, *5*, 109–114. https://doi.org/10.3390/hemato5020009

Academic Editor: Antonino Carbone

Received: 1 February 2024
Revised: 13 March 2024
Accepted: 19 March 2024
Published: 26 March 2024

1. Introduction

Selective IgA deficiency (IgA-D) is defined as a serum IgA less than 7 mg/dL, in patients older than 4 years with normal levels of immunoglobulins G and M [1]. The prevalence of IgA-D varies among different ethnicities, being 1:163 in Spain and between 1:500 and 1:1000 in the USA [2].

IgA-D has been historically considered a high-risk entity for developing allergic/anaphylactic transfusion reactions (AATRs) [3,4]. The most severe reactions have been related to class-specific antibodies in complete IgA-D patients after transfusion of plasma-containing blood components [4]. IgA deficiency is mentioned in transfusion guidelines and different recommendations exist to transfuse patients affected by this immunodeficiency [5,6]. As a general principle in transfusion therapy, IgA-D has remained the main indication to wash blood components in order to avoid adverse reactions [6]. Our hospital also included it in the local transfusion guidelines. However, AATR reactions related to IgA deficiency

are extremely low. The annual incidence of anaphylactic reactions was 32 out of nearly 2.2×10^6 blood components issued in the UK in 2021 [7]. Only one of these patients had an IgA-D. The other three patients with IGA-D suffered febrile non-hemolytic reactions. In consistency with these data, it has been suggested that the IgA-D-related anaphylactic transfusion reaction is not evidence based [8]. Then, the IgA-D condition remains a controversial issue in transfusion medicine.

The objective of this retrospective study was to collect information about epidemiology, AATRs, and transfusion management in patients with IgA-D in a tertiary care hospital.

2. Methods

We conducted three different approaches to collect evidence about epidemiology, AATRs, and transfusion management of patients with IgA-D at La Fe University Hospital. First, we analysed the prevalence of IgA-D in a population of patients diagnosed with acute leukaemia and treated at our hospital. We chose this population due to their high transfusion requirements. IgA-D was diagnosed according to the European Society for Immunodeficiencies criteria [1].

The second approach consisted of collecting transfusion data from IgA-D patients. For this purpose, a list of patients whose diagnosis was IgA-D was obtained through the Documentation Service of the Hospital. The IgA levels were reviewed and a blood bank database was consulted to find out how many IgA-D patients had received blood products and if they suffered any adverse transfusion reaction.

Finally, we reviewed all the patients recorded in the hemovigilance system suffering an AATR in our hospital from January 2000 to January 2023. We retrospectively reviewed the AATRs that occurred within the first 6 h after the start of transfusion and were classified as mild or severe. Mild AATRs include symptoms such as pruritus and skin rash that are controlled with antihistamines and, in most cases, allow the transfusion to continue. Severe AATRs are considered life-threatening and produce serious symptoms, such as facial angioedema, stridor, respiratory compromise, hypoxemia, and hypotension. The clinical evaluation was performed by the attending physician, who recorded information about AATR characteristics, IgA level when performed, blood product implicated, and administered treatment.

IgA determination was required by the physician who assessed the AATR or, more frequently, by the blood bank responsible. IgA was performed by nephelometry using different devices over the years. Anti-IgA was not performed in any case since this test is not available at our hospital.

The statistical analysis was performed with SPSS (version 15, SPSS Inc., Chicago, IL, USA). Categorical variables were compared by means of the Chi-square test or Fisher's exact test. The Mann–Whitney U-test for continuous variables was used to compare the groups when applicable. A value of $p < 0.0.05$ was considered significant.

3. Results

3.1. IgA-D prevalence in Hematologic Patients

We reviewed the IgA levels of 1023 patients (591 men and 432 women) diagnosed with acute leukaemia from January 2010 to January 2019. The median age was 57 years (range, 19–91). IgA levels at diagnosis were available for 669 patients, and 2 had IgA-D. The prevalence was 1 in 334 patients. Among the transfused patients with normal IgA (n = 667), AATR reactions were reported in 85 (12.7%), and none occurred in the two patients with IgA-D. Washed platelets and red blood cells were transfused to one IgA-D patient as highly recommended by the hospital in which the patient was first treated.

3.2. Transfusion in Patients with IgA-D

A total of 276 patients were diagnosed with IgA-D at our hospital: 143 men and 133 women. The median age was 16.5 years (range, 4–84). Patients were mostly from internal medicine (15.9%), pediatric rheumatology (12.6%), and pediatric digestive medicine

(10.8%) services. A total of 187 (67.75%) had IgA-D (<7 mg/dL), while 89 (32.25%) had IgA levels between 7 mg/dL and 60 mg/dL. Twenty-one patients with IgA-D and ten patients with low IgA levels received at least one blood component (Table 1). Plasma was transfused to eight IgA-D patients while six patients received red blood cells, platelets, and plasma. Two IgA-D patients received anti-D immunoglobulins. No adverse reactions were reported in any patient.

Table 1. Transfusion burden in patients with IgA deficiency and low IgA levels. Results are expressed as median and range.

Blood Components	IgA < 7 mg/dL *n* = 21	IgA 7–60 mg/dL *n* = 10
Red blood cells	5 (1–56)	19 (2–43)
Fresh frozen plasma	3.5 (1–21)	4 (1–12)
Platelet concentrates	7.5 (1–65)	10.5 (1–27)

3.3. Allergic/Anaphylactic Transfusion Reaction Characteristics and IgA Levels

For a 23-year period, 813,123 blood components were issued to La Fe University Hospital patients, and 670 allergic/anaphylactic transfusion reactions were reported to the hemovigilance Unit (1 in 1214 blood components transfused). AATRs occurred in 325 men and 264 women, with a median age of 52 years (range, 2–94). More than one AATR (range, 2–12) was reported in 53 patients. Characteristics of adverse transfusion reactions are shown in Table 2. The most frequent clinical manifestations were pruritus and skin rash. Severe reactions occurred in 56 patients (1/14,520 components) who developed symptoms and signs that were assessed by the physician as life-threatening. IgA determination was performed on 423 patients, with 375 and 48 suffering a mild and severe reaction, respectively. The median (range) IgA levels were 215 mg/dL (4–5570) for mild reactions and 214 mg/dL (14–824) for severe reactions (p = ns). Only one patient had IgA levels lower than seven. This patient had received allogeneic hematopoietic stem-cell transplantation 1 month before, had no IgA-D diagnosis but a post-transplantation transient immunodeficiency, and received a standard transfusion. The blood component most frequently related to the AATR was platelet concentrate (n = 380, 56.7%), followed by fresh frozen plasma (n = 145, 21.6%).

Most patients (n = 42) who had suffered a severe AATR continued to receive standard blood components. Premedication with steroids and antihistamines was used in all of them. In addition, transfusion lasted 4 h using an infusion pump in some cases, at the discretion of the haematologist in charge. Washed platelet concentrates were administered to 2 patients who developed severe and repeated AATRs, despite premedication. Both had normal IgA levels. Surprisingly, one of these two patients received standard FFP without an adverse reaction. There were no deaths related to AATRs.

Table 2. Characteristics of allergic/anaphylactic reactions after blood transfusion (AATRs).

Signs and Symptoms	Mild AATRs (*n* = 614)	Severe AATRs (*n* = 56)
Pruritus	307	16
Urticaria	193	9
Skin rash	331	25
Nausea/vomiting	60	13
Fever	70	0
Dyspnea	61	31
Angio-edema	9	4
Bronchospasm	9	10
Shock	0	9
Hypotension	25	20

Table 2. *Cont.*

Signs and Symptoms	Mild AATRs (n = 614)	Severe AATRs (n = 56)
Treatment		
Blood component		
Platelet concentrate	350	30
Fresh frozen plasma	129	16
Red blood cells	116	4
Hematopoietic progenitors	16	4
Not reported	3	2
Antihistamines	122	1
Corticosteroids	36	7
Antihistamines + steroids	296	30
Acetaminophen	19	0
Antihistamines + steroids + pethidine	4	5
Pethidine	8	0
Adrenalin	0	6
Not reported	129	6

4. Discussion

Contradictory information is available on the risk of AATRs in IgA-D patients with anti-IgA [8,9]. Consequently, concern remains about the potential for life-threatening anaphylactic reactions in IgA-D patients, and it has become a challenge for transfusion services. Our study provides data that questions the relevance of the IgA-D-related anaphylactic transfusion reaction entity in the routine transfusion practice. A striking finding is that patients with IgA-D can receive a high number of transfusions of different blood components and not be at greater risk for adverse events. Taking into account the incidence of IgA-D among Spanish people (1/100–200) [10], we can assume that quite a few patients suffering from this condition have been routinely transfused at our hospital without problems over the years. Our data are consistent with this statement by showing uneventful and continued transfusion of standard blood components to 23 IgA-D patients. We are aware of the scarce number of IgA-D cases, which is a limitation of this study.

Since the first case of anaphylactoid transfusion reaction was reported and associated with anti-IgA in 1968 [11] to the present, more than 40 additional cases have been published [8,12–14]. Patients who suffered severe AATRs had no detectable IgA and produced very high titers of specific anti-IgA. The postulated mechanism involves complement activation and the generation of endogenous anaphylotoxins [15]. Consequently, IgA-D was considered a high-risk entity for suffering ATTRs, and the washing of blood components was established for patients with documented IgA-D [16,17]. AATRs are among the most common transfusion reactions, with the reported incidence (1/1500) being quite lower than that found in our study (1/332). Plasma proteins are most often implicated in AATRs, and, therefore, plasma and platelet transfusions are most commonly associated with AATRs [11]. Most AATRs are mild or moderate, while severe allergic/anaphylactic reactions are reported only in 1.2 to 5.9 per 100,000 components transfused [1,7,18]). The higher incidence found in our study could be explained by different criteria for severe AATRs definition among Transfusion Services. If we consider "severe" as only those cases who received adrenalin for treatment, then the incidence of severe AATRs is quite lower (1/135,520) and similar to other Hemovigilance Systems [18].

The results of a 23-year-period study in our hospital support the rarity of IgA-D-related AATRs. In fact, we did not detect any IgA-D related to AATR. It has to be focused on that available platelets at our hospital are suspended in additive solution and contain little plasma. The results from the last British hemovigilance system reports are consistent with our findings showing that anaphylactic reactions associated with IgA-D patients are exceptional [5,7,19–21]. There were no allergic reactions clearly associated with IgA-D in

2020 when 2,074,517 blood components were issued in UK Blood services and 54 severe allergic/anaphylactic reactions were reported [20]. In 2022 (2,224,696 blood components transfused), 36 severe allergic reactions were reported that required the use of adrenaline. In addition, there were five reactions reported in patients who were subsequently discovered to have a severe IgA deficiency. Four were febrile reactions involving marked systemic upset, and the fifth one showed hypotension. There is no information about anti-IgA levels. Note that none of these reactions in IgA-D patients had allergic characteristics [21]. In 2015, none of the 12 patients investigated for anaphylactic transfusion reactions at the Canadian Blood Services was found to have anti-IgA, while in 2016, only 1 of 9 patients investigated was found to have anti-IgA [5]. Then, the exact cause for most severe AATRs remains undetermined, but it seems clear that most IgA-D patients with or without anti-IgA antibodies will not experience severe reactions with standard blood-component transfusion.

Different results from ours have been published by Anani and Cols [22], who determined the number of AATRs in patients with IgA-D following the transfusion of standard components compared with IgA-replete transfusion recipients. Among 39 IgA-D patients who received blood-component transfusion, 4 (10%) suffered a severe allergic transfusion reaction, while only 8 AATRs were reported amongst 1545 (0.52%) IgA-replete transfusion recipients. These authors concluded that IgA-D patients have an increased risk of severe allergic transfusion reactions. The clinical manifestations of severe allergic transfusion reactions were urticaria and hypoxemia (n = 4), hypotension (n = 3), and facial oedema (n = 2). Anti-IgA was not performed in any case in which the causal relationship could not be confirmed.

Management of severe allergic/anaphylactic transfusion reactions is similar for patients with or without IgA-D. Current guidelines recommend washing blood components for those patients suffering severe anaphylaxis in patients with confirmed IgA-D and a history of transfusion reactions. If a life-saving transfusion is needed, standard blood components should be transfused with observation in a clinical area within the facilities to treat an acute severe reaction [23]. In our opinion, these recommendations also apply to patients without IgA-D. In fact, the only two patients in whom washed platelets were transfused at our hospital suffered severe and repetitive AATRs, but had normal IgA levels, and had a good response to washed platelet transfusion.

The safety of patients is the main concern when administering a blood transfusion. The risk–benefit balance must always be evaluated, but measures to decrease risks should be evidence-based. Quite the contrary, the consideration of IgA-D as a high-risk condition can lead to unnecessary transfusion delays and blood-component manipulation.

5. Conclusions

In summary, since the AATRs related to IgA-D are extremely low, as reported in current hemovigilance systems [20,21], IgA-D should not be considered as a high-risk entity to develop AATRs. On the contrary, our findings support standard transfusion management of IgA-D patients without previous adverse transfusion reactions, as long as clinical monitoring of the transfusion is guaranteed.

Author Contributions: Conceptualization: P.S.; data curation: A.B., A.B.G., P.A.C., M.S., and M.J.M.; formal analysis: P.S.; drafting and critical revision: J.d.l.R. and I.G.-S. All authors have read and agreed to the published version of the manuscript.

Funding: This study was not supported by any sponsor or funder.

Institutional Review Board Statement: This study protocol was reviewed and approved by the Research Ethics Committee of La Fe University Hospital (Reference 2142_23).

Informed Consent Statement: Written informed consent was not required, since this is a retrospective study.

Data Availability Statement: All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Conflicts of Interest: The authors have no conflicts of interest to declare.

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