Editorials

IgA deficiency: what we should—or should not—be doing

Although IgA deficiency (IgAD) is currently recognised as the most frequent immunodeficiency in humans,[1] individuals with IgAD are largely considered to be healthy and when discovered are usually not investigated further or followed up.[2] The rare occasion when IgAD is a cause for concern is when these individuals require blood or blood products, in which case current practice advises that products not containing IgA must be administered. On these occasions it is also often, but not always, practice to check for the presence of anti-IgA antibodies, the importance of which is still frequently disputed (vide infra[3]).

Are we doing what we should? Are the above practices justified by currently existing data?

What are the clinical consequences of IgAD?

Total IgAD is defined in most studies as selectively undetectable IgA at a value of 0.05 g/litre. However, there is no consensus regarding this value and some UK referral centres are now moving the cut off point to 0.0016 g/litre by using more sensitive techniques.[4] The limit of sensitivity differs greatly depending on the method used, namely: 0.2 g/litre for nephelometry, 0.05 g/litre for low level radial immunodiffusion plates, and 0.0016 g/litre for haemaglutination inhibition techniques. Partial IgAD refers to detectable but reduced IgA, more than 2 SD below the low end of age matched, normal range values, and this is mostly seen in children under 5 years of age; about half of these children reach normal values by 14 years (transient IgAD).[2] The data discussed below refer to total IgAD unless stated otherwise.

Although we consider IgAD to be the most frequent immune deficiency (found in one in 700 healthy blood donors), it must be stressed that this applies only to the Western world because the prevalence differs with ethnic background, and is only one in 18 500 among Japanese blood donors.[1] Most studies suggest that up to two of three individuals with IgAD are healthy,[2] but it must again be emphasised that these conclusions were largely based on studies looking at healthy blood donors, in whom IgAD was found during initial screening with no follow up. Recent long term follow up of initially healthy IgAD individuals shed a completely different light on this assumption, demonstrating that as many as 80% may develop symptoms over the years.[5] In addition, there is now evidence that IgAD is part of the spectrum of primary antibody deficiency syndromes that spans IgA/IgG subclass deficiency through to common variable immunodeficiency (CVID).[1 6] Familial inheritance has been shown in 25% of individuals, suggesting a strong genetic influence, which is supported by the mapping of susceptibility genes to the major histocompatibility complex (MHC) class III regions.[7] Those individuals with IgAD who develop symptoms will suffer from synopulmonary infections, allergies, autoimmune diseases, gastrointestinal diseases, especially coeliac disease,[8 9] as well as gut and lymphoid malignancies.[1 2]

How frequently are anti-IgA antibodies found?

One of the most important issues regarding IgAD is the recognition that some patients lacking IgA will develop serious, life threatening adverse reactions upon receiving blood or blood products containing IgA, and that these reactions are in many cases associated with anti-IgA antibodies.[10] In patients with IgAD, the frequency of anti-IgA antibodies has been reported to be from 20% to 40%,[11 12] with a recent large UK study giving a frequency of 32% or about one in three.[4] The frequency in patients with CVID is about 29%,[4] but is by far the highest in patients with both IgAD and IgG subclass deficiency—reportedly over 60%.[13] In individuals with partial IgAD, most authors fail to detect anti-IgA antibodies,[13] and the importance of these antibodies when detected is unknown. Importantly, anti-IgA antibodies can also be detected in normal human sera and have been reported to have a very broad range of frequencies (from 2% to 59%).[4 14] These discrepancies probably result from the various methods and cut off points used when detecting IgA antibodies, and leave us without a true picture of the importance of anti-IgA antibodies.

How important is the isotype of anti-IgA antibody considered?

Anti-IgA antibodies are usually of the IgG class but can also be IgM or IgE.[12 15] Anti-IgA antibodies can be of broad specificity, usually class specific (anti-α chain, found almost exclusively in patients with total IgAD and largely thought to be responsible for anaphylactic reactions),[16] or of limited specificity, usually allotype specific.[16] Several authors have reported an association of severe anaphylactic transfusion reactions with high titres of IgE antibodies.[11 12] Other studies have either not been able to detect IgE anti-IgA antibodies at all,[13] or have concluded that they are not likely to be important because direct skin prick testing with IgA in a patient with IgE anti-IgA antibodies and a previous adverse reaction was negative.[16] It has also been pointed out that patients with IgAD often have undetectable serum IgE, rendering the production of IgE anti-IgA antibodies unlikely.[17] It has been suggested that in individuals lacking serum IgE, antibodies against ruminant IgG may be responsible for false positive results in assays for detecting IgE anti-IgA antibodies.[17] In addition, some authors argue that clinically adverse reactions often do not have the characteristics of a bona fide IgE mediated anaphylactic reaction (there is often a prolonged time of onset, lack of systemic symptoms such as hypotension, no difficulty in breathing, etc).[10] However, in other reported cases the anaphylactic character of the reaction cannot be disputed.[12 18] Taken together, the clinical relevance of IgE anti-IgA antibodies remains controversial and necessitates further clarification.

Are anti-IgA antibodies clinically relevant?

The importance of anti-IgA antibodies in inducing and predicting adverse reactions remains controversial. This issue reflects on all patients receiving blood or blood products and has become more important since the wider use of

intravenous immunoglobulin (IVIG) as a substitution treatment for humoral immunodeficiencies as well as an immunomodulatory agent in autoimmune diseases.[19 20] A recent large study from the National Blood Service in Sheffield[4] demonstrates that far fewer individuals with IgAD and anti-IgA antibodies develop transfusion reactions than would be expected if anti-IgA antibodies were always involved: the frequency of transfusion reactions was approximately one in 30 000; the frequency of patients with IgAD was approximately one in 900, and anti-IgA antibodies were detected in about one third of these. These data imply that only one in 30 patients with IgAD or one in 100 patients with IgAD and anti-IgA antibodies develop reactions after receiving IgA containing blood. Taken together, the importance of anti-IgA antibodies in patients with IgAD remains unclear and a summary of available data demonstrates the following:

(1) Numerous studies suggest that high titre, class specific IgG antibodies are often but not always associated with adverse reactions.[4]
(2) The presence of anti-IgA antibodies in a patient is neither sufficient nor essential to cause adverse reactions[4 5]: in one study, 76% of patients with reactions had anti-IgA antibodies whereas 21% had reactions without having antibodies.[21] Alternatively, blood containing anti-IgA antibodies has been given to patients with IgAD with no adverse effects.[4 14 18]
(3) Anti-IgAD antibodies are not consistently induced by exposure to IgA containing products.[5]
(4) Certain studies have shown that anti-IgA antibody titres remain rather constant over time,[5] although personal experience suggests that this may vary among patients.
(5) The existence of anti-IgA antibodies is a poor predictor of adverse reactions.[10–13]
(6) Severe anaphylactic transfusion reactions have been associated with high titres of IgE antibodies, although other studies have not been able to detect IgE.[11 12]
(7) Recent important studies have shown that immunodeficient patients lacking IgA (IgAD, IgA/IgG subclass, and CVID) with a high titre of anti-IgA antibodies can be given low IgA IVIG (270 mg/litre and 790 mg/litre) repeatedly, with no adverse effects.[22 23] This is also the case with individuals who have IgAD and are receiving IVIG for immunomodulatory purposes.[24] Intriguingly, recent reports suggest that patients with IgAD can tolerate subcutaneously administered IVIG with a very high IgA content (5 g/litre), and even show the disappearance of anti-IgA antibodies in some cases.[25 26]

Conclusion

Data on current practices regarding IgAD are incomplete but show that practices vary widely. This is largely the result of insufficient available knowledge and consequent lack of evidence based clinical protocols. Many issues mentioned above are still open and in need of further study. The major questions that remain unresolved are the following: which investigations should we perform in individuals in whom we find IgAD and should we monitor these patients over the years? Should we check IgA and/or anti-IgA antibody concentrations in all patients about to receive blood or blood products? Which anti-IgA antibodies in terms of isotype and specificity should we test for? If anti-IgA antibodies are detected, should their titres be monitored? Is the use of low IgA IVIG justified in all patients with IgAD, irrespective of high costs?

Proposal

It would obviously be difficult to establish a consensus viewpoint in the absence of further relevant studies. Therefore, we propose to form a study group, under the auspices of the newly established UK Primary Immunodeficiency Network (UK PIN), which would organise further investigations along two lines: first, a national questionnaire based survey would be conducted aimed at defining in sufficient detail the state of the art practices in the UK regarding IgAD; second, a multicentred prospective study would be organised to investigate the importance of anti-IgAD antibodies in anaphylactic reactions to blood or blood products containing IgA. Based on these findings, the study group would compile a formal, evidence based consensus clinical protocol for managing patients who have IgAD and anti-IgA antibodies.

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