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 haemagglutination 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 Western world because the prevalence di...
intravenous immunoglobulin (IVIG) as a substitution treatment for humoral immunodeficiencies as well as an immunomodulatory agent in autoimmune diseases. A recent large study from the National Blood Service in Sheffield 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.

(2) The presence of anti-IgA antibodies in a patient is neither sufficient nor essential to cause adverse reactions: in one study, 76% of patients with reactions had anti-IgA antibodies whereas 21% had reactions without having antibodies. Alternatively, blood containing anti-IgA antibodies has been given to patients with IgAD with no adverse effects. 

(3) Anti-IgAD antibodies are not consistently induced by exposure to IgA containing products.

(4) Certain studies have shown that anti-IgA antibody titres remain constant over time, although personal experience suggests that this may vary among patients.

(5) The existence of anti-IgA antibodies is a poor predictor of adverse reactions.

(6) Severe anaphylactic transfusion reactions have been associated with high titres of IgE antibodies, although other studies have not been able to detect IgE.

(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.

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.

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-IgA 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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References


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