Complete antibody deficiency (IgM, IgA and IgG) correlates with a higher prevalence of bronchiectasis

John P Hodkinson PhD[1], Cathy Bangs BSc (Hons)[2], Matthew Buckland[3], David Guzman[4], Patrick Yong[5], Sorena Kiani-Alikhan[5]

1. Biotest UK Ltd 2. Central Manchester University Hospitals NHS Foundation Trust 3. Bart's Health NHS Trust 4. University College London 5. Royal Surrey and Frimley Park NHS Foundation trusts

Corresponding Author:

John Hodkinson, Biotest UK Ltd, 1st Floor Park Point, 17 High St, Longbridge, Birmingham, B31 2UQ

Tel. 00 44 121 733 3393 Email. john.hodkinson@biotest.com Fax. 00 44 121 733 3066

Sources of funding:

Biotest UK Ltd funded statistical analysis by an independent statistician

Capsule Summary:

This interrogation of a large mulitcentre, national database revealed an association between complete antibody deficiency (low IgM, IgA and IgG) and the prevalence of bronchiectasis in PAD patients receiving adequate IgG replacement. It also showed that a high proportion of patients (>75%) are affected by IgM and IgA deficiency in addition to IgG.

Key words: IgM, IgA, bronchiectasis, immunoglobulin, CVID, primary immunodeficiency, primary antibody deficiency

To the Editor,

In the majority of primary antibody deficiency (PAD) patients receiving adequate IgG replacement, the risk of serious infections is reduced, however a significant proportion continue to suffer from recurrent respiratory tract infections and even have episodes of pneumonia[1,2]. It is known that IgA and IgM are physiologically important for protecting the mucosal surfaces and therefore it has been suggested that IgA and/or IgM deficiency may create a permissive mucosal environment for development of infective complications in PAD patients adequately replaced with IgG[3,4]. Our hypothesis is that patients with IgA and IgM deficiency are at increased risk of infective complications at mucosal sites and therefore investigated this question using data from the United Kingdom Primary Immunodeficiency (UKPID) registry. The UKPID registry is a national database of primary immunodeficiency (PID) patients in the UK which currently holds data on the diagnosis, symptoms and treatment of 3673 PID patients from 36 hospitals.

Patient data was extracted from the UKPID registry based upon a number of inclusion and exclusion criteria. Patients were included only if they had been receiving immunoglobulin replacement for any PAD for 2 years, had a recorded IgG titre at diagnosis, were over the age of 4 and had a current IgG trough level of >5g/l. Greater than 5g/l was specified as it is considered the minimum adequate trough level, although it is clear than much higher trough levels are frequently required based upon medical need[5]. Patients were excluded if they did not consent for commercial companies to access their anonymised data, if the treating centre did not reply to the request for approval to release the data, they were deceased or lost to follow-up at the time of data collection or had a pre-treatment IgG trough greater than 5g/l. These criteria yielded 628 suitable patients and included the following parameters: Current and pre-treatment IgG, IgA and IgM titres, diagnosis, dose, route of administration, frequency of administration as well as the outcomes bronchiectasis and use of prophylactic antibiotics. Bronchiectasis was chosen as the primary endpoint as it is indicative of long term infective respiratory complications and is associated with significant morbidity[6]. The secondary outcome was “current use of prophylactic antibiotics” which was intended as a surrogate for current infective complications. Both endpoints were expressed as a binary outcome 'yes or no'.

The cohort was split into two groups for all analyses based on IgA and/or IgM titre - IgA deficiency was considered <0.8g/l and IgM deficiency was considered to be <0.5g/l. These thresholds were selected as they reflect the cut-off for the 5th centile of serum immunoglobulin concentration in the UK population[7]. The chi-squared t-test was used to determine if the prevalence of either binary outcome was significantly different in patients with low and normal IgA and /or IgM.

In this study the presence of bronchiectasis and the use of prophylactic antibiotics (clinical indicators) will be correlated with the IgG, IgA and IgM titres.

The statistical analyses to be performed were decided prior to the unblinding of the data and were undertaken by an independent statistician following patient, hospital and ethics committee consent.

87% of patients included in the analysis were diagnosed with common variable immunodeficiency (CVID) and the remaining PADs included X-linked agammaglobulinaemia (XLA), specific antibody deficiency (SPAD), IgG subclass deficiency, IgA deficiency, thymoma with immunodeficiency and other hypogammas. Patients treated with both intravenous and subcutaneous immunoglobulin were included.

Complete antibody deficiency correlates with a higher prevalence of bronchiectasis

Table 1 shows the percentage of patients in each group who have been diagnosed with bronchiectasis. The table shows that the prevalence of bronchiectasis was higher in patients with IgA and/or IgM deficiency. The IgA and/or IgM deficiency is in addition to IgG deficiency which was present in all patients. The higher prevalence of bronchiectasis was most pronounced in patients with IgA and IgM deficiency with a bronchiectasis prevalence of 47% versus 32% (relative risk increase 46%; absolute risk increase of 15%; p-value 0.002). This group were considered to have complete antibody deficiency as IgM, IgA and IgG were all below the normal range.

IgA/IgM levels did not consistently correlate with the use of prophylactic antibiotics

The data showed a statistically significant increase in prophylactic antibiotic use in patients with normal IgA compared to those with IgA deficiency however there was no correlation in the low IgM group or in the IgM and IgA deficiency group. This is likely to be due to the lack of national consensus in the UK on prescribing prophylactic antibiotics in PAD and is likely to reflect multiple different trust policies and clinician preferences. 47% of the patients in this cohort were receiving prophylactic antibiotics at the time of data extraction as shown in Figure 1.

The prevalence of bronchiectasis in this cohort is ~44%

The prevalence of bronchiectasis found in this cohort of patients with PAD was 43.5% (Figure 1) and is similar to previously reported data from the ESID registry and is consistent with the literature precedent from large UK centres (48-66%)[1]. The data also showed that those patients diagnosed with bronchiectasis had lower IgA and IgM titres when compared to those patients without bronchiectasis, however this was only found to be statistically significant for IgM.

~75% of the cohort is IgG, IgM and IgA deficient

Figure 1 shows that 75.8% of this cohort had complete antibody deficiency at diagnosis. This complete antibody deficiency persisted to the most recent measurement in the same patients with the same prevalence. The low IgA and IgM titres are in addition to IgG deficiency which up to now has been the focus of research and clinical practice.

The data shows a correlation between complete antibody deficiency and a higher prevalence of bronchiectasis. Due to the nature of the analysis causality cannot be assumed, however the absence of both immunoglobulin classes which are responsible for mucosal defence suggests a plausible contributory mechanism of pathology for PAD patients suffering recurrent respiratory infections.

This study indicates that bronchiectasis is a common feature in PAD and also shows that a high percentage of patients are IgM, IgA and IgG deficient which we propose may contribute to this outcome.

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