J Clin Immunol (2017) 37:329–331
DOI 10.1007/s10875-017-0381-y

LETTER TO EDITOR

Low IgA and IgM Is Associated with a Higher Prevalence of Bronchiectasis in Primary Antibody Deficiency

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Received: 22 August 2016 / Accepted: 2 March 2017 / Published online: 14 March 2017

To the Editor,

In the majority of primary antibody deficiency (PAD) patients receiving IgG replacement therapy (IgGRT), the risk of serious infections is reduced; however, a significant proportion continue to have upper and lower respiratory tract infections [1]. It is thought 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 some PAD patients who appear to be adequately replaced with IgG [2–4]. Our hypothesis is that patients with IgA and IgM deficiency are at increased risk of infective complications at mucosal sites and therefore we investigated this question using data from the United Kingdom Primary Immunodeficiency (UKPID) registry. The UKPID registry is a national database of primary immunodeficiency patients in the UK which currently holds data on the diagnosis, symptoms and treatment of 4086 patients from 35 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 intravenous or subcutaneous immunoglobulin replacement (IVIg or SCIg) 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 >5 g/l. Greater than 5 g/l was specified as it is considered the minimum adequate trough level, although it is clear that much higher trough levels are frequently required based upon medical need and 96% of included patients had a trough of >6 g/l and 82% had a trough of >8 g/l at the last measurement [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, the patient was deceased or lost to follow-up at the time of data collection or had a pre-treatment IgG level greater than 5 g/l. These criteria yielded 626 suitable patients and included the following parameters: Current and pre-treatment IgG, IgA and IgM titres, diagnosis, dose of IgGRT, route of administration, frequency of IgGRT administration as well as the two outcomes of 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 divided based on IgA and/or IgM titres. IgA deficiency was defined as IgA < 0.8 g/l and IgM deficiency was defined as IgM < 0.5 g/l. These thresholds were selected as they reflect the cut-off for the fifth centile of serum immunoglobulin concentration in the general UK population

The original version of this article was revised: The family name of Andrea Wartenberg-Demand was misspelled as Watenberg-Demand.

Electronic supplementary material The online version of this article (doi:10.1007/s10875-017-0381-y) contains supplementary material, which is available to authorized users.

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[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 or the use of prophylactic antibiotics (clinical indicators) was investigated in relation to IgG, IgA and IgM levels. The statistical analyses performed were decided prior to collection of the data and were undertaken by an independent statistician following patient, hospital and ethics committee consent. Eighty-nine percent of patients included in the analysis were diagnosed with common variable immunodeficiency (CVID) and the remaining PADs were X-linked agammaglobulinaemia (XLA), thymoma with immunodeficiency, hyper IgM syndrome and other forms of hypogammaglobulinemia (see Table 1). Patients treated with either IVIg or SCIg were included.

Complete Antibody Deficiency Is Associated with a Higher Prevalence of Bronchiectasis

The cohort was separated into four groups based on IgA and IgM level at diagnosis. The four groups were characterised as follows: patients with low IgA only, patients with low IgM only, all patients with either normal IgA and/or normal IgM and finally all patients with both low IgA and low IgM. Figure 1 shows the percentage of patients in each group who have been diagnosed with bronchiectasis. This graph shows that the prevalence of bronchiectasis was higher in patients who had both IgA and IgM deficiency (48% compared to 33% in patients with normal IgA and/or IgM (relative risk increase 45%; absolute risk increase of 15%; *p* value 0.0012)), in addition to IgG deficiency (<5 g/l) which was being treated with IgG replacement therapy in all patients.

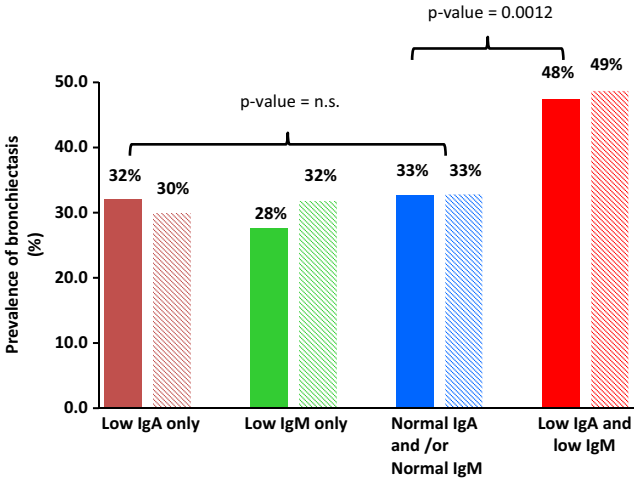

Fig. 1 The prevalence of bronchiectasis is compared between groups of patients based on IgA and IgM levels at diagnosis. The prevalence of bronchiectasis was significantly higher only in the group of patients who had both low IgA and low IgM (for whole cohort $p = 0.0012$; for CVID only $p = 0.0012$). The *solid bars* show the prevalence for the whole cohort and the *patterned bars* show the prevalence in the CVID cohort only. Low IgA was defined as <0.8 g/l and low IgM was defined as <0.5 g/l

Table 1 The demographic characteristics of the cohort. All patients had IgG levels of <5 g/l at diagnosis. The patients were grouped based on the IgA and IgM levels measured at diagnosis. Values for the CVID-only cohort are in brackets. Please note that the values for IgA and/or IgM were not available for 14 patients

	No. of patients	Percent
Diagnosis		
CVID	559	89
XLA	20	3
Thymoma with immunodeficiency	11	2
Hyper IgM syndrome	2	0.3
Other hypogammaglobulinaemia	34	5
Immunoglobulin levels		
Low IgA only (<0.8 g/l)	87 (77)	14 (14)
Low IgM only (<0.5 g/l)	29 (22)	5 (4)
Low IgA and IgM	453 (414)	72 (74)
Normal IgA and/or IgM	159 (134)	25 (24)
Outcome measures		
Diagnosed with bronchiectasis	266 (249)	43 (45)
Receiving prophylactic antibiotics	294 (262)	47 (47)
Total	626	100

The difference in bronchiectasis prevalence between patients with normal IgA or IgM and patients with normal IgA and IgM was not statistically significant. This suggests that normal levels of either IgA or IgM are sufficient to render the observed effect while normal levels of both are not necessary. However, this conclusion comes with the caveat that the group 'normal IgA and IgM' was small and therefore the lack of significance may be due to sample size.

IgA/IgM Levels Were Not Associated with the Use of Prophylactic Antibiotics

The analysis did not show any statistically significant difference in prophylactic antibiotic use when patients were stratified by the levels of IgA and/or IgM (data not shown). This could be due to the lack of national consensus in the UK on prescribing prophylactic antibiotics in PAD and is likely to reflect multiple different hospital policies and clinician preferences. The data showed that 47% of the patients were receiving prophylactic antibiotics at the time of data extraction (Table 1). However, the proportion of patients with bronchiectasis who were on antibiotics was significantly higher than those without bronchiectasis; 53.9 vs 43.3% ($p = 0.006$).

The Prevalence of Bronchiectasis in this Cohort Is ~43%

The prevalence of bronchiectasis found in this cohort of patients was 43% (Table 1) which is similar to previously reported data from the ESID registry and is consistent with other literature from large UK centres (48–66%) [1]. Patients diagnosed with bronchiectasis had significantly lower levels of both IgA and IgM at diagnosis, when compared to those patients without bronchiectasis (the mean levels with or without bronchiectasis for IgA were 0.36 vs 0.43 g/l ($p = 0.003$), respectively and for IgM were 0.36 vs 0.53 g/l, respectively ($p = 0.001$)). The mean IgG level was also lower in patients with bronchiectasis compared to patients with no bronchiectasis (2.06 vs 2.67 g/l; $p = 0.00001$).

Seventy-two percent of the Cohort Is IgG, IgM and IgA Deficient

Table 1 shows that 72% of this cohort had low IgA and IgM in addition to low IgG at diagnosis. We also noted that the majority of patients affected by IgA and IgM deficiency at diagnosis continued to be deficient in IgA and IgM at the most recent measurement. The most recent measurements for IgA and IgM were higher compared to the time of diagnosis in only a small proportion of the patients (for IgA in 13% and for IgM in 17%) but in a comparable number of patients, these values had reduced (reduced IgA in 13% and IgM in 18% of patients). This data suggests that IgG replacement does not have any discernible effect on production/catabolism of endogenous IgA and IgM in PAD patients.

The data shows an association between combined IgA and IgM deficiency and a higher prevalence of bronchiectasis. Due to the nature of the analysis, causality cannot be assumed; however, the data is in keeping with the proposed IgA role in mucosal defence and it is in line with a body of evidence that suggests a significant role for IgM in protection against recurrent lower respiratory tract infections in PAD which are commonly by encapsulated bacteria [8].

In summary, this study indicates that a deficiency in IgM and IgA (in addition to IgG) is a common feature of PAD and also suggests that the presence of normal levels of IgA or IgM may be a favourable indicator against the development of bronchiectasis.

Acknowledgments We would like to acknowledge the medical, nursing and administrative staff of the following centres from which the UKPIN registry collected the data used in this study. University Hospitals Birmingham NHS Foundation Trust, Heart of England NHS Foundation Trust, Sandwell and West Birmingham Hospitals NHS Trust, Royal Brompton & Harefield NHS Foundation Hospitals, Cambridge University Hospitals NHS Foundation Trust, Papworth Hospital NHS Foundation Trust, Cardiff and Vale University Health Board, Dudley Group NHS Foundation Trust, Epsom & St Helier University Hospitals NHS Trust, Frimley Park & Royal Surrey County NHS Foundation Trusts, NHS Greater Glasgow and Clyde, Great Ormond Street Hospital NHS Foundation Trust, Hull & East Yorkshire Hospitals NHS Trust, The Leeds Teaching Hospitals NHS Trust, Royal Liverpool Hospitals NHS Trust, Central Manchester University Hospitals NHS Foundation Trust, The Newcastle Upon Tyne Hospitals NHS Foundation Trust, University Hospitals of North Midlands NHS Trust, Nottingham University Hospitals NHS Trust, Oxford University Hospitals NHS Foundation Trust, Plymouth Hospitals NHS Trust, Royal Free London NHS Foundation Trust, Salford Royal NHS Foundation Trust, Sheffield Children's NHS Foundation Trust, Sheffield teaching Hospitals NHS Foundation Trust, University Hospital Southampton NHS Foundation Trust, St George's University Hospitals NHS Foundations Trust. We would also like to thank Mr. Patrick Dubovy for reviewing the statistical analysis.

Compliance with Ethical Standards

Conflict of Interest Matthew Buckland, Catherine Bangs and David Guzman declare that they have no conflict of interest. John P Hodkinson, Andrea Wartenberg-Demand, Artur Bauhofer and Patrick Langohr are employees of Biotest AG that manufactures IgM and IgA rich immunoglobulins. Patrick Yong and Sorena Kiani-Alikhan were previously on Biotest AG advisory board.

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