

Original Article

Immunoglobulin E deficiency: a forgotten clue pointing to possible immunodeficiency?

David J Unsworth, Paul F Virgo and Robert J Lock

Immunology and Immunogenetics, Blood Sciences Laboratory, North Bristol NHS Trust, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK

Corresponding author: David J Unsworth. Email: joe.unsworth@nbt.nhs.uk

Abstract

Background: Patients with primary antibody deficiency often have delayed diagnosis. Very low IgE, found during investigations for allergy, may be a marker for other immunodeficiency.

Method: We introduced a new laboratory policy of testing cases with very low IgE levels for possible linked antibody deficiency. The data represent an audit of routine results collected over two years.

Results: Very low IgE (≤ 2 IU/mL) was identified in 85/2622 (3.2%) routine patient samples. Two children and four adult patients were found to have one or more classes of immunoglobulin below the reference range for age. In 2/6, the initiative of the laboratory led to a new unsuspected diagnosis of antibody immunodeficiency.

Conclusions: Common variable immunodeficiency continues to be overlooked as a primary cause of lung disease in adults. Very low serum IgE should trigger appropriate investigation (immunoglobulin quantification and serum electrophoresis).

Ann Clin Biochem 2011; 1–3. DOI: 10.1258/acb.2011.011052

Introduction

Antibody immunodeficiency leads to significant increased risk of bacterial and some other infections. Diagnostic delay is common in antibody deficiencies, with the mean being 3.5 y in the UK.¹ Complications of infection, including bronchiectasis, nasal sinus damage and poor lung function, are therefore commonplace by the time diagnosis is eventually confirmed.²

In some cases being investigated for atopic disorders, the unexpected finding of very low IgE might be a marker of other underlying antibody immunodeficiency. This might be either primary or secondary immune paresis, the latter, for example, caused by drug therapy or lymphoproliferative disorders. The common denominator is recurrent sinus or respiratory tract bacterial infection, arising because of antibody immunodeficiency, but with a clinical presentation mimicking possible allergic disease. Routine diagnostic investigations in this context typically include a total serum IgE in addition to other tests, including IgE to specific allergens (most often *Aspergillus fumigatus*); a raised total IgE concentration supporting an atopic disposition. In these circumstances the implications of finding a very low serum IgE may be overlooked.

There have been few studies on patients with low IgE. Smith *et al.*³ reviewed 44 adult patients with IgE < 2.5 IU/mL and found 57% of these to have other immunoglobulin

abnormalities. García *et al.*⁴ identified 11 children aged 16 months to 10 y with IgE < 5 IU/mL and found only one to have another immunoglobulin defect, IgA deficiency. Others have also described patients with IgE and other immunoglobulin deficiency.^{5–8}

The data presented here represent a review of our findings in patients with very low IgE.

Method

As part of an audit process, we reviewed results on all 2771 routine samples submitted for total serum IgE quantification to the Bristol Immunology and Immunogenetics laboratory over a two-year period between December 2008 and November 2010. Just prior to this period, we had introduced a new laboratory policy of testing cases with very low IgE levels for possible linked antibody deficiency. Repeat analyses were excluded from the analysis, leaving 2622 samples for review.

Where hypogammaglobulinaemia was identified, we reviewed the patients' case-notes in detail.

As controls we quantified total serum IgE in 20 known antibody-deficient patients (18 common variable immunodeficiency [CVID], 1 CVID with granulomata, 1 hypogammaglobulinaemia with increased polyclonal IgM). In addition, total IgE was quantified on serum samples from

Table 1 Immunoglobulins in patients with very low IgE and other antibody deficiency

Patient	Age (y)	Source	IgE (kIU/L)	IgG (g/L)	IgA (g/L)	IgM (g/L)	Reason for test
1	0.8	Tertiary referral	<2 (<14)	1.39* (3.0–10.9)	<0.25 (0.2–0.7)	<0.18 (0.60–2.1)	Cystic fibrosis
2 [†]	6.0	Tertiary referral	2 (<85)	2.70 (5.4–16.1)	0.39 (0.40–2.0)	0.63 (0.50–2.1)	Recurrent sino-pulmonary infection
3	24.8	Respiratory medicine	<2 (<113)	8.68 (6.0–16.0)	<0.06 (0.80–4.0)	1.63 (0.50–2.00)	Bronchiolitis
4 [†]	54.3	Respiratory medicine	<2 (<113)	2.64 (6.0–16.0)	<0.24 (0.80–4.0)	<0.17 (0.50–2.00)	Possible ABPA, Proximal bronchiectasis
5	63.2	General medical practice	<2 (<113)	2.92 (6.0–16.0)	<0.24 (0.80–4.0)	0.25 (0.40–2.00)	Bronchiectasis
6	73.4	Respiratory medicine	<2 (<113)	6.43 (6.0–16.0)	1.96 (0.80–4.0)	0.36 (0.40–2.0)	Bronchiectasis

Age-related reference ranges are in parentheses

ABPA, allergic bronchopulmonary aspergillosis

*Subsequently shown to be low for all subclasses but IgG2 strikingly low at <0.15 g/L (reference range 0.30–3.27 g/L)

[†]Denotes the two cases where laboratory initiative, based on further investigation of low IgE, led to a confirmed diagnosis of clinically significant immunodeficiency and a related change in patient management

19 random patients with paraproteinaemia (7 myeloma, 12 monoclonal gammopathy of undetermined significance [MGUS], [including 2 high-risk MGUS]).

Results

Very low IgE (≤ 2 IU/mL) was identified in 85/2622 (3.2%) routine patient samples. Only 38/85 had been checked for serum immunoglobulins based on our new trial laboratory policy (3/20 children less than 18 years of age, 35/65 adults). Six of 38 (2/20 [10%] children, 4/65 [6.2%] adults) patients were found to have one or more classes of immunoglobulin below the reference range for age (Table 1). In two of these six cases, the initiative of the laboratory led to a new unsuspected diagnosis of antibody immunodeficiency. A further 550/2622 (21.0%) had low normal IgE (2.1–20 IU/mL).

Distribution of IgE concentrations in the control populations is shown in Table 2.

The majority of known cases of antibody deficiency, but not all, also had serum IgE ≤ 2 IU/mL. Three patients with paraproteinaemia had serum IgE ≤ 2 IU/mL. The paresis seen was not related to paraprotein concentration. Of note, the patient with the highest paraprotein concentration (60 g/L IgG-kappa) had serum IgE 11.9 IU/mL. In contrast, a patient with MGUS (6 g/L IgG-lambda) had serum IgE <2 IU/mL.

Table 2 Distribution of IgE concentrations in control groups

Patient group	Number in group	IgE ≤ 2 IU/mL (very low)	IgE 2.1–20 IU/mL (low normal)	IgE > 20 IU/mL
Antibody immunodeficiency*	20	17 [†]	2	1 [‡]
Myeloma	7	1	6	0
Monoclonal gammopathy of undetermined significance	12	2	5 (1 high risk)	5 (1 high risk)

*Eighteen common variable immunodeficiency (CVID), 1 CVID with granulomata, 1 hypogammaglobulinaemia with increased polyclonal IgM

[†]Includes patients with CVID and granulomata

[‡]Patient with hypogammaglobulinaemia with increased polyclonal IgM

Discussion

We found 6/38 patients investigated had immunoglobulin deficiencies (IgA, IgG and/or IgM), in addition to a low serum IgE. This is a much lower incidence than described in other series³ but nonetheless represents a significant detection rate (16%).

Two children with very low IgE had hypogammaglobulinaemia. The first (Patient 1, Table 1) had cystic fibrosis (CF). Reactive hypergammaglobulinaemia is typical in CF, but hypogammaglobulinaemia is found in a minority of children with CF,⁹ although it is not necessarily a poor prognosis feature.^{10,11} This child was also shown to be IgG2 deficient, as is seen in a significant minority of patients with CF.⁹ Since the time of the original analysis the patient's immunoglobulins, including IgE, have steadily improved. The second (Patient 2, Table 1) was under investigation for recurrent sino-pulmonary infections at the time of referral. Our investigations confirmed a primary immunodeficiency, which is still undefined at this time.

Four adults with very low IgE who had hypogammaglobulinaemia were identified. No consistent pattern was seen: one isolated low IgM (Patient 6), one selective IgA (Patient 3) and two consistent with CVID (Patients 4 and 5, Table 1). Of interest, all presented with lung disease, three being through the Respiratory Medicine team. This has been shown in a UK audit to be the most common route of referral.¹² We found no cases of paraproteinaemia in the study group. However, there were three patients within the paraprotein control group with very low IgE, confirming our hypothesis that in some cases secondary immune paresis could theoretically present with very low IgE. In order to detect all cases of myeloma via this route, our data suggest all serum samples with IgE ≤ 20 IU/mL would need serum protein electrophoresis. As this encompasses 24.2% of our patients, it is unlikely to be a cost-effective proposition.

The control data demonstrate that a minority of patients with primary antibody deficiency still has detectable serum IgE (3/20; 15%, Table 2). This has been a variable finding in the literature,^{13–15} with our data in keeping with those of Spitz *et al.*¹⁴ and Waldmann *et al.*¹⁵ Our data indicate that we could not confidently detect 100% of CVID patients via this route and that some cases will still be overlooked, leading to further diagnostic delay.

Selective IgA deficiency is found in one in 400–500 of the general population.^{16,17} With this exception, antibody deficiencies are rare disorders (e.g. CVID, 1 in 10,000) and as such often not recognized early in the disease process.^{2,18}

In summary, we have shown that CVID continues to be overlooked as a primary cause of lung disease in adults and, in view of the high morbidity associated with this disorder, very low serum IgE (≤ 2 kIU/L) should trigger appropriate investigation (immunoglobulin quantification and serum electrophoresis).

DECLARATIONS

Competing interests: None.

Funding: None.

Ethical approval: Not applicable.

Guarantor: DJU.

Contributorship: All authors contributed to the planning, writing and approval of final draft.

Acknowledgements: None.

REFERENCES

- 1 Seymour B, Miles J, Haeney M. Primary antibody deficiency and diagnostic delay. *J Clin Pathol* 2005;**58**:546–7
- 2 Björkander J, Bake B, Hanson LÅ. Primary hypogammaglobulinaemia: impaired lung function and body growth with delayed diagnosis and inadequate treatment. *Eur J Resp Dis* 1984;**65**:529–36
- 3 Smith JK, Krishnaswamy GH, Dykes R, Reynolds S, Berk SL. Clinical manifestations of IgE hypogammaglobulinemia. *Ann Allergy Asthma Immunol* 1997;**78**:313–8
- 4 García POS, López TJJ, Gómez VJ. IgE deficiency: a forgotten disease? *Rev Allerg Mex* 2009;**56**:192–7
- 5 De Laat PC, Weemaes CM, Gonera R, Van Munster PJ, Bakkeren JA, Stoelinga GB. Clinical manifestations in selective IgA deficiency in childhood. A follow-up report. *Acta Paediatr Scand* 1991;**80**:798–804
- 6 Out TA, Van Munster PJ, De Graeff PA, Thé TH, Vossen JM, Zegers BJ. Immunological investigations in individuals with selective IgA deficiency. *Clin Exp Immunol* 1986;**64**:510–7
- 7 Hammarström L, Smith CI. IgG2 deficiency in a healthy blood donor. Concomitant lack of IgG2, IgA and IgE immunoglobulins and specific anti-carbohydrate antibodies. *Clin Exp Immunol* 1983;**51**:600–4
- 8 Hammarström L, Holm G, Palmblad J, Persson MA, Smith CI. Lack of IgG in a healthy adult: a rare case of dysgammaglobulinemia with undetectable serum IgG, IgA2, and IgE. *Clin Immunol Immunopathol* 1984;**30**:1–10
- 9 Garside JP, Kerrin DP, Brownlee KG, Gooi HC, Taylor JM, Conway SP. Immunoglobulin and IgG subclass levels in a regional pediatric cystic fibrosis clinic. *Pediatr Pulmonol* 2005;**39**:135–40
- 10 Wheeler WB, Williams M, Matthews WJ Jr, Colten HR. Progression of cystic fibrosis lung disease as a function of serum immunoglobulin G levels: a 5-year longitudinal study. *J Pediatr* 1984;**104**:695–9
- 11 Matthews WJ Jr, Williams M, Oliphant B, Geha R, Colten HR. Hypogammaglobulinemia in patients with cystic fibrosis. *N Engl J Med* 1980;**302**:245–9
- 12 Spickett GP, Askew T, Chapel HM. Management of primary antibody deficiency by consultant immunologists in the United Kingdom: a paradigm for other rare diseases. *Qual Health Care* 1995;**4**:263–8
- 13 McLaughlan P, Stanworth DR, Webster AD, Asherson GL. Serum IgE in immune deficiency disorders. *Clin Exp Immunol* 1974;**16**:375–81
- 14 Spitz E, Gelfand EW, Sheffer AL, Austen KF. Serum IgE in clinical immunology and allergy. *J Allergy Clin Immunol* 1972;**49**:337–47
- 15 Waldmann TA, Polmar SH, Balestra ST, Jost MC, Bruce RM, Terry WD. Immunoglobulin E in immunologic deficiency diseases. II. Serum IgE concentration of patients with acquired hypogammaglobulinemia, thymoma and hypogammaglobulinemia, myotonic dystrophy, intestinal lymphangiectasia and Wiskott-Aldrich syndrome. *J Immunol* 1972;**109**:304–10
- 16 Koistinen J. Selective IgA deficiency in blood donors. *Vox Sang* 1975;**29**:192–202
- 17 Holt PD, Tandy NP, Anstee DJ. Screening of blood donors for IgA deficiency: a study of the donor population of south-west England. *J Clin Pathol* 1977;**30**:1007–10
- 18 Blore J, Haeney MR. Primary antibody deficiency and diagnostic delay. *BMJ* 1989;**298**:516–7

(Accepted 1 April 2011)