



BRIEF COMMUNICATIONS

Elevated total serum immunoglobulin E (>1000 IU/mL): implications?

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Abstract

Atopic eczema, allergic broncho-pulmonary aspergillosis, helminthic infections and rare primary immunodeficiencies are known to elevate total serum immunoglobulin E (IgE) above 1000 IU/mL. However, of 352 patients with IgE >1000 IU/mL seen in our hospital over a 5-year period, less than 50% had these conditions. Markedly elevated IgE levels in the rest of the patients were associated with asthma, allergic rhinitis and food allergy, instances where the test is of limited diagnostic utility.

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Serum immunoglobulin E (IgE) can be raised because of allergic diseases, helminthic infections, inflammatory conditions, malignancies and immunodeficiency.¹ Extreme elevation of total serum IgE above 1000 IU/mL is typically associated with only a few conditions: atopic eczema,² allergic broncho-pulmonary aspergillosis³ (ABPA), helminthic infection⁴ and rare primary immunodeficiencies.⁵

We sought to determine the proportion of patients with total serum IgE >1000 IU/mL attributable to atopic eczema and the well known but rarer causes mentioned above, and to describe the other associated conditions observed in our study cohort. A cross-sectional analysis of markedly elevated total serum IgE in an unselected population has not previously been described.

We retrospectively audited laboratory records at our tertiary university hospital in Melbourne, Australia to identify patients with total serum IgE measured between 1 January 2010 and 31 December 2014. Patients with total serum IgE >1000 IU/mL were included in the study. This level was selected as a cut-off value based on current diagnostic criteria for ABPA.³ Total serum IgE was measured on the ImmunoCap 250 (Thermo Scientific, Uppsala, Sweden). This audit was approved by the Alfred Health Ethics Committee (Reference number 338/15), and requirement for informed consent was waived.

Clinical records were reviewed to identify conditions associated with raised total serum IgE. The conditions were broadly grouped under the following categories: 'Allergy', 'Infection', 'Inflammation', 'Immunodeficiency', 'Neoplastic' and 'Miscellaneous'.

A condition was considered to be associated with the raised total serum IgE if:

1. The condition was documented as such by an allergy specialist and/or
2. The condition was shown in previous literature to be associated with raised serum IgE.

Subjects were labelled 'undetermined' when no explanation for the raised total serum IgE was documented.

Data were analysed using SPSS (Version 22.0, IBM, Armonk, NY, USA). Non-parametric data were compared using one-way analysis of variance, and associations between two variables were analysed using Spearman's rank correlation. Categorical variables are reported as number (percentage) and continuous variables are reported as median (interquartile range (IQR)). A two-sided *P* value <0.05 was taken to be statistically significant.

Total serum IgE was measured in 5599 patients over the 5-year period. Three hundred and fifty-two patients (6.3%) had total serum IgE >1000 IU/mL. One hundred and sixty-three patients were male (46.3%), and the median age was 38 (IQR 27–58) years. As detailed in Table 1, 167 patients (47.4%) had atopic eczema, ABPA, helminthic infections or hyper-IgE syndrome – conditions typically associated with total serum IgE >1000 IU/mL.

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Table 1 Conditions associated with total serum IgE >1000 IU/mL

Associated conditions	Frequency (<i>n</i> = 352)
Conditions typically associated with total serum IgE >1000 IU/mL (<i>n</i> = 167)	
Atopic eczema	129 (36.6%)
ABPA	33 (9.4%)
Helminthic infection (Strongyloides infection)	4 (1.1%)
Primary immunodeficiency (hyper-IgE syndrome)	1 (0.3%)
Other conditions (<i>n</i> = 185)	
Allergy (excluding atopic eczema and ABPA)	
Asthma	92 (26.1%)
Allergic rhinitis	84 (23.9%)
Food allergy	49 (13.9%)
Infection	
Aspergillus sinusitis	2 (0.6%)
Aspergilloma	1 (0.3%)
HIV	1 (0.3%)
Viral pneumonia	1 (0.3%)
Inflammation	
Urticarial vasculitis	1 (0.3%)
ANCA-associated vasculitis	1 (0.3%)
Rheumatoid arthritis	1 (0.3%)
Bullous pemphigoid	1 (0.3%)
Miscellaneous	
Chronic idiopathic urticaria	3 (0.9%)
Isolated angioedema	2 (0.6%)
Systemic mastocytosis	1 (0.3%)
Eosinophilic oesophagitis	1 (0.3%)
Orofacial granulomatosis	1 (0.3%)
Undetermined	22 (6.2%)

ABPA, allergic broncho-pulmonary aspergillosis; ANCA, anti-neutrophil cytoplasmic auto-antibody; HIV, human immunodeficiency virus; IgE, immunoglobulin E.

Among these conditions, atopic eczema was the most common. The rest of the patients had conditions that were less commonly associated with extreme elevations of serum IgE levels (other allergic conditions, non-helminthic infections, various inflammatory and miscellaneous conditions) or no clear cause.

Allergic conditions accounted for the majority of conditions associated with serum IgE >1000 IU/mL (87.5%). The allergic conditions identified in our cohort were asthma, allergic rhinitis, atopic eczema, food allergy and ABPA; 110 (40%) patients had one identifiable allergic condition, while 97 (35.3%), 47 (17.1%) and 21 (7.6%) had two, three or four co-existing allergic conditions respectively. The number of co-existing allergic conditions did not correlate significantly to the total serum IgE ($r = 0.104$, $P = 0.084$). Note that patients with ABPA were excluded from this analysis as 84.8% of patients with ABPA had asthma.

To determine the extent of increase in serum IgE attributable to individual allergic conditions, we examined the

subgroup of patients with only one allergic condition. Patients with ABPA and atopic eczema had the highest levels of total serum IgE (Table 2).

Ninety-five of the 129 patients with atopic eczema (73.6%) had clinically active eczema at the time of sampling, and their IgE levels were similar to those with inactive disease. Of the 164 asthma patients without ABPA, 71 (43.3%) had uncontrolled asthma requiring escalation of treatment, and their IgE levels were similar to those with controlled asthma. Among patients with allergic rhinitis, 45 (29.6%) had seasonal symptoms only, and 46 (30.3%) had perennial symptoms with seasonal exacerbations. Total serum IgE testing was performed in spring and summer months in 42.9% of the patients with seasonal rhinitis symptoms ($n = 91$), and their levels were similar to that of patients sampled during autumn and winter months.

Non-allergic conditions accounted for only 44 (12.5%) of our cohort. Nine patients had underlying infection. The most common infections were helminthic infections (serological evidence of exposure to *Strongyloides*) and culture-proven *Aspergillus*-related respiratory tract infections. Inflammatory conditions were seen in four patients: urticarial vasculitis, anti-neutrophil cytoplasmic auto-antibody-associated vasculitis, rheumatoid arthritis and bullous pemphigoid. Other miscellaneous conditions were chronic idiopathic urticaria, angioedema, systemic mastocytosis, eosinophilic oesophagitis and orofacial granulomatosis.

The cause for elevated total serum IgE was not evident in 22 patients. Eight patients were under investigation for prior adverse reactions to drugs or insect bites. Two patients had underlying cystic fibrosis and positive serum-specific IgE to *Aspergillus* but did not otherwise meet criteria for ABPA diagnosis.

Less than half of the patients with total serum IgE >1000 IU/mL in our cohort had conditions typically associated with this degree of IgE elevation – that is, atopic eczema, ABPA, helminthic infections and

Table 2 Total serum IgE in patients with a single allergic condition†

Allergic condition	Frequency (<i>n</i> = 131)	Median IgE (IQR) IU/mL
Asthma-associated ABPA	21 (16%)	2613 (1524–4634)
Asthma without ABPA	32 (24.4%)	1843 (1202–3356)
Eczema	25 (19.1%)	2512 (1286–5925)
Allergic rhinitis	29 (22.1%)	1467 (1093–2093)
Food allergy	24 (18.3%)	1383 (1151–1795)

†One-way analysis of variance $P < 0.01$. ABPA, allergic broncho-pulmonary aspergillosis; IgE, immunoglobulin E; IQR, interquartile range.

hyper-IgE syndrome. The rest of the cohort generally had allergic conditions other than atopic eczema and ABPA.

We demonstrated that markedly raised total serum IgE >1000 IU/mL may be associated with allergic conditions other than atopic eczema, namely asthma, allergic rhinitis and food allergy. The elevated IgE level in these conditions is of limited diagnostic utility. High levels of IgE have previously been observed in patients with asthma and have also been associated with increased asthma severity.^{6,7} One previous study reported high levels of total serum IgE >1000 IU/mL in a minority of patients with allergic rhinitis.⁸

The marked elevation of total serum IgE in patients with food allergies was interesting as this has not been well described. One explanation could be the presence of undocumented Th2 'drivers', such as eczema, which can be associated with food allergy.⁹ Due to the design of our audit, we also could not exclude the possibility of spectrum bias as large numbers of food-allergic patients may have undergone IgE testing at our institution. Our results may therefore not be applicable to patients with food allergies in general.

Helminths are known to induce Th2 immunity. Viruses including cytomegalovirus, Epstein–Barr virus and human immunodeficiency virus have also been found to increase serum IgE levels.^{1,10,11} One patient in our study was human immunodeficiency virus positive with no previous allergic diseases and a negative parasite screen. Another patient in our study had a clinical diagnosis of viral pneumonia. Other non-allergic conditions were uncommon in our study.

A very high total serum IgE has direct diagnostic utility in very few conditions, namely ABPA, hyper-IgE syndrome and helminthic infection. Total serum IgE >1000 IU/mL is a major diagnostic criterion for ABPA,³ and serum IgE is also incorporated into a clinical scoring system for evaluating patients with suspected hyper-IgE syndrome.¹² A raised total serum IgE is a useful

screening tool for patients with suspected helminthic infection, especially if there is no previous history of atopy.⁵ However, these conditions were present in only a small fraction of our cohort.

For most allergic conditions, total serum IgE has limited diagnostic utility but may have contextual utility in specific instances. First, in patients with high serum IgE, the presence of atopic eczema has explanatory value and usually obviates the need for further investigations. However, there is typically no clear mandate for ordering a serum total IgE measurement initially. Second, in patients with rhinitis, a high total serum IgE predicts allergen sensitisation, supporting an allergic rather than non-allergic aetiology for rhinitis.¹³ However, a diagnosis of allergic rhinitis is best supported by the detection of specific IgE to allergens relevant to the clinical history. Third, in patients with food allergies, the ratio of allergen-specific IgE to total serum IgE has predictive value for outcomes of oral food challenges.^{14,15}

We recognise certain limitations in our study. First, diagnostic accuracy depended on explicit clinical documentation in the case notes. Second, we were unable to ascertain that the raised serum IgE was fully explained by the single ascribed condition documented in the medical records. Third, our study was conducted in a tertiary hospital with a very large specialist allergy service, so our results may not be generalisable to other populations. Fourth, as we set out to examine patients with total serum IgE >1000 IU/mL, we cannot extrapolate our results to subjects with a lower total serum IgE level.

In conclusion, extreme elevations in total serum IgE are not limited to the widely recognised causes of atopic eczema, ABPA, helminthic infections and primary immunodeficiencies. Markedly elevated IgE levels may also be associated with other allergic conditions, in which the direct diagnostic utility is limited. Clinicians should be judicious in requesting the test and circumspect when interpreting elevated readings.

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The use of low-dose sodium valproate in the management of neuropathic pain: illustrative case series

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Abstract

Anti-epileptic drugs are commonly used in the management of neuropathic pain. Sodium valproate, however, is an anti-epileptic drug that is not commonly used. We report four patients with neuropathic pain who responded very well to the initiation of low-dose oral sodium valproate. Low-dose sodium valproate may have a role in managing neuropathic pain, especially when other first-line agents are unsuccessful or relatively contraindicated.

Neuropathic pain is a disabling condition that may lead to chronic pain. Its pathophysiology stems from a series of events that cause electrical hyper-excitability in somatosensory pathways, similar to epileptic seizures.¹ As a result, anti-epileptic drugs are commonly used in the management of neuropathic pain.

Current Australian recommendations for neuropathic pain management include the use of anti-depressants and anti-epileptic medications, including amitriptyline (tricyclic anti-depressants), duloxetine (serotonin noradrenaline reuptake inhibitor), gabapentin (anti-epileptic) and pregabalin (anti-epileptic). Anti-epileptic agents are thought to work by decreasing excitability of neurons at

a spinal and brain level and possibly increasing the effectiveness of the other major inhibitory network involving gamma-aminobutyric acid (GABA). Gabapentin and pregabalin are thought to modify the action of voltage-gated calcium channels of sensory nerves and, through this mechanism, interfere with the release of substance P, noradrenaline and the excitatory glutamate neurotransmitter.²

Opioids are mentioned, but the guideline states that stronger doses are required as the nature of neuropathic pain is not as responsive to narcotic analgesics, and the evidence is limited to peripheral neuropathic conditions. Tramadol, a weak opioid, with serotonin and noradrenaline reuptake inhibitor actions and, more recently, tapentadol are also options that are considered in the management of neuropathic pain.²

In Australia, pregabalin and gabapentin are the only anti-epileptic medication that has been approved and

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