

Patterns of Allergic Sensitization in High IgE Syndromes

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Abstract Dramatic elevations in the serum IgE level are seen both in polygenic allergic diseases such as atopic dermatitis and food allergy, and in a growing list of monogenic primary immune deficiencies (PIDs). Although the IgE produced in patients with PID has generally been considered to be driven by dysregulated IL-4 production and thus lack antigen specificity, in fact allergen-specific IgE can be detected by skin and serum testing in many of these patients. However, perhaps not surprisingly given the distinct immunologic pathways involved, the patterns of allergic disease and atopic sensitization vary widely between syndromes, leading to strikingly different clinical phenotypes.

Keywords IgE · Specific IgE · Primary immunodeficiency · Allergy

Introduction

Although IgE represents only a fraction of the total serum immunoglobulin pool, it is of central importance in allergic disease. In healthy, non-atopic adults, serum IgE ranges between 0–200 IU/ml [1]. Dramatic elevations in the serum IgE level (>1000 IU/ml) are seen both in polygenic allergic diseases such as atopic dermatitis and food allergy, and in a growing list of monogenic primary immune deficiencies (PIDs) (Table 1) [15]. Although some overlap exists, these

represent immunologically distinct pathways. Therefore, it is not surprising that the patterns of allergic disease and atopic sensitization vary between syndromes, leading to strikingly different clinical phenotypes.

Patterns of Allergic Sensitization

Autosomal Dominant (AD) Hyper IgE Syndrome (HIES) Due to Mutations in STAT3

AD-HIES, or Job's Syndrome, is a rare PID characterized by recurrent skin and lung infections, connective tissue abnormalities, and dramatically elevated IgE typically >10,000 IU/ml [6]. It was described in 2007 as being due to autosomal dominant negative mutations in signal transducer and activator of transcription 3 (STAT3), a transcription factor involved in the signaling pathway for multiple cytokines including IL-6, IL-10, and IL-12 family members [21]. The exact mechanism driving the elevation in IgE is still not clearly known, although reduced production of IFN- γ and IL-10 with unregulated IL-4 production has been proposed [15].

Interestingly, despite the dramatic elevations in IgE, clinically apparent allergic disease and anaphylaxis are rare, particularly when compared to patients with atopic dermatitis and similarly elevated levels of IgE [22]. This has been hypothesized by various authors to be due to lack of antigen specificity of the IgE (so called junk IgE) driven by dysregulated IL-4 production [23], lower affinity of the IgE due to extra-germinal center production of IgE and failure to undergo affinity maturation [24], or to a mast cell intrinsic defect reducing IgE/high affinity IgE receptor (Fc ϵ RI)-mediated degranulation [22, 25].

It has long been noted that patients with HIES are capable of producing antigen-specific IgE, as 13 of 17 patients were

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Table 1 PIDs associated with high IgE

PID	Gene defect
ADA-SCID ^a	ADA [2]
Atypical complete DiGeorge syndrome ^a	22q11.2 deletion [3]
X-linked hyper IgM syndrome ^a	CD40L [4]
Comèl-Netherton syndrome	SPINK5 [5]
Hyper IgE syndrome (HIES)	STAT3 (AD-HIES) [6] DOCK8 (AR-HIES) [7, 8]
IL-21/IL-21 receptor deficiency	IL21 [9], IL21R [10]
Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX)/IPEX-like syndrome	FOXP3 [11], STAT1 [12]
Inborn errors of TIR pathway	IRAK-4, MYD88 [13]
MALT1 deficiency ^a	MALT1 [14]
Omenn syndrome (OS)	Hypomorphic mutations in RAG, ARTEMIS, IL-7R, RMRP, IL-2R γ , ZAP70, ADA, DNA Ligase IV [15]
PGM3 deficiency	PGM3 [16]
Phospholipase C γ 2-associated antibody deficiency and immune dysregulation (PLAID)	PLCG2 [17]
Prolidase deficiency	PEPD [18]
Wiskott-Aldrich syndrome (WAS)	WASP [19], WIP [20]

ADA adenosine deaminase, AD autosomal dominant, AR autosomal recessive, DOCK8 dedicator of cytokinesis 8, IRAK-4 interleukin-1 receptor-associated kinase, MALT1 mucosa-associated lymphoid tissue lymphoma translocation gene 1, MyD88 myeloid differentiation factor, PGM3 phosphoglucomutase 3, SPINK5 serine protease inhibitor, Kazal type 5, SCID severe combined immunodeficiency, STAT3 signal transducer and activator of transcription 3, TYK2 tyrosine kinase 2, WASP WAS protein, WIP WASP-interacting protein

^a Reported only occasionally, not a feature in all patients

found to have high titer IgE against *Staphylococcus aureus* and 12 of 17 to have IgE against *Candida albicans* [23]. This sensitization was not detected in atopic controls, patients with parasitic infections, patients with other immunodeficiencies characterized by recurrent infections with these pathogens, or normal controls. Presence of anti-pathogen IgE did not correlate with disease severity, or with total IgE level. This provided some of the first evidence that, while the IgE production was dysregulated, it retained antigen specificity.

Within the past 3 years, new data has been published on the IgE repertoire of patients with HIES, highlighting important differences compared to controls with atopic dermatitis. One study of seven patients with AD-HIES revealed overall only mild to moderate atopy: mild-moderate eczema (median scoring atopic dermatitis (SCORAD) score of 20.3), absence of asthma, delayed reactions to medications, mild allergic rhinoconjunctivitis, and mild food allergy without anaphylaxis [26]. This finding is particularly remarkable given the dramatic elevation in total IgE (median 6000 IU/ml, range 4062–106,320 IU/ml). Consistent with the mild clinical allergic phenotype, the median aeroallergen-specific IgE was only 0.7 IU/ml with a very small wheal on skin testing; this was directed towards *D. pteronyssinus* and *D. farinae* as well as cat dander (Table 2). Food allergen-specific IgE testing and skin testing

was negative. This is in striking contrast to patients with autosomal recessive (AR)-HIES, discussed below with high titer IgE to foods, and patients with atopic dermatitis who despite having similarly elevated levels of total IgE (median 8208.5 IU/ml, range 1056–18,344 IU/ml), had high titer IgE largely directed against perennial and seasonal aeroallergens with some sensitization to foods. The authors therefore postulate that the IgE in patients with AD-HIES is “largely not directed to allergens.”

Similar findings were reported in abstract form using Immuno Solid-phase Allergy Chip (ISAC) microarray to analyze sera from 60 HIES and 60 atopic dermatitis patients [36]. Despite equivalent total serum IgE concentrations, HIES patients had a much more limited repertoire of detectable allergen-specific IgE compared to atopic dermatitis patients, with the most notable difference being significantly lower rates of sensitization to aeroallergens.

A larger study of 71 patients with AD-HIES followed at the National Institutes of Health (NIH) reached a different conclusion, however [22]. This cohort had similarly elevated median IgE levels (7079 IU/ml) to patients included in the above studies, but the authors found that many patients were capable of producing food allergen specific IgE (egg, milk, and peanut) in amounts well above published 95 % positive predictive value

Table 2 Patterns of allergic sensitization in high IgE syndromes

Syndrome	Total IgE (IU/ml)	IgE specificity
ADA-SCID	0–2800 [2]	• Sensitization to perennial but not seasonal aeroallergens • IgE variably present to food allergens
Atopic dermatitis	200–30,000 [22, 26]	• High titer IgE to perennial and seasonal aeroallergens • IgE present to pathogen <i>S. aureus</i> enterotoxin A and B [27], and colonizing fungi <i>M. furfur</i>, <i>C. albicans</i>, and <i>T. rubrum</i> [28] • IgE present to multiple food allergens at low to high titers, with variable clinical severity [26]
AD-HIES due to mutations in STAT3	400–100,000 [22, 26]	• Very low titer IgE to perennial aeroallergens; no sensitization to seasonal aeroallergens [26] • IgE present to pathogens <i>C. albicans</i> and <i>S. aureus</i> [23] • IgE variably present to food allergens [22]
AR-HIES due to mutations in DOCK8	400–100,000 [7, 26, 29]	• Very low titer IgE to perennial aeroallergens; no sensitization to seasonal aeroallergens. [26] • IgE present to multiple food allergens at moderate-high titer, with high clinical severity [26]
Comèl-Netherton Syndrome	>900 [30]	• Sensitization on skin prick testing to perennial and seasonal aeroallergens and foods [30]
IRAK-4/MyD88 deficiency	10–17,400 [13]	• Detectable aeroallergen and food specific IgE at low titer
IPEX	40–30,000 [31]	• Positive serum allergen testing and skin prick tests to food and environmental allergens has been reported [32–35]

levels. This sensitization did not however correlate with a clinical history of food allergy anaphylaxis, as only 38 % of patients with AD-HIES had immediate hypersensitivity to food and 8.5 % had food-induced anaphylaxis, compared to 58.3 and 33.3 %, respectively, in controls with atopic dermatitis and similarly elevated levels of IgE. The authors go on to demonstrate impaired mast cell degranulation and basophil activation, implicating a mast cell intrinsic defect as the cause for reduced clinically significant food allergy and anaphylaxis. Importantly, this does not rule out the concurrent possibility that the IgE, while antigen specific and present in high titer, is of lower affinity or avidity.

Thus, the data available to date indicate that some, but not all, patients with AD-HIES have detectable environmental, food, and microbial antigen specific IgE that ranges from low to very high titer, but this does not correlate with an increased risk of clinically significant atopy and represents a modest proportion of the total IgE. This is similar to the pattern seen in atopic dermatitis, in which the sum of all measurable antigen specific IgE does not add up to the total IgE.

AR-HIES Due to Mutations in DOCK8

AR-HIES due to loss of function of DOCK8 shares many overlapping features with AD-HIES, including recurrent skin and lung infections and marked elevations in serum IgE (typically >5000 IU/ml). However, patients also uniquely have significant recurrent cutaneous viral infections (herpes simplex virus, herpes zoster, molluscum contagiosum, human papillomavirus) as well as increased risk of malignancy. They

lack the connective tissue disease more commonly seen in AD-HIES. Almost all patients with DOCK8 mutations are severely atopic, with a high prevalence of severe food allergies, asthma, and atopic dermatitis (median SCORAD 69.0), and some with environmental allergies [7, 8, 26].

In the only published study that has examined patterns of IgE sensitization in six DOCK8 patients, the median aeroallergen-specific IgE was 0.12 IU/ml, with only sensitization to *D. pteronyssinus* identified [26]. This is similar to what is seen in AD-HIES but much different than the high-titer environmental aeroallergen-specific IgE seen in atopic dermatitis patients. In contrast, the food allergen-specific IgE in patients with DOCK8 was quite elevated at 27.5 IU/ml, higher than that seen in patients with atopic dermatitis. Unlike AD-HIES, this high titer food-allergen specific IgE does correlate with the presence of clinically severe food allergy and anaphylaxis. Evaluation of the allergic phenotype in a larger cohort of DOCK8 patients followed at the NIH is currently in progress (personal communication, Jonathan Lyons).

The molecular mechanism behind the dramatic elevation in IgE in DOCK8 patients has not been clearly established. However, DOCK8 is a guanine exchange factor (GEF) that catalyzes nucleotide exchange on Cdc42, a Rho-GTPase recently shown to be required for antigen-stimulated mast cell degranulation via the high affinity IgE receptor FcεRI [37]. Thus, one would predict a similar lack of IgE-mediated anaphylaxis similar to that seen in AD-HIES; this is not borne out clinically however. Interestingly, two recent reports describe that food allergy in DOCK8 patients is not cured by hematopoietic stem

cell transplantation, even when full donor chimerism in peripheral blood is achieved [38, 39]. Further investigations are necessary to characterize the mechanism of atopy in this cohort.

Comèl-Netherton Syndrome

Comèl-Netherton syndrome is an autosomal recessive disorder characterized by congenital ichthyosis, the hair shaft defect trichorrhexis invaginata, and atopic disease. It is due to mutations in serine protease inhibitor Kazal-type 5 (SPINK5), encoding the serine protease inhibitor lympho-epithelial Kazal-type 5-related inhibitor (LEKTI) that has been proposed to downregulate desquamation and affect T cell maturation [40]. These patients have been speculated to have chronic antigenic stimulation due to an impaired skin and gut barrier, with an exaggerated Th2/IgE response [30], but at least one study has failed to demonstrate Th2 cytokine skewing in the serum so the exact mechanism of IgE elevation remains unclear to date [40].

A review of 44 cases reported elevated IgE >900 IU/ml in 11 % (geometric mean of 4751 IU/ml), asthma and/or allergic rhinitis in 34 % and food allergy in 32 % [30]. In that series, about a quarter had positive skin or serum allergy testing to environmental and seasonal aeroallergens and foods. A more recent review of nine patients reported eczema in 8 (89 %), food allergy in 7 (78 %), allergic rhinitis in 5 (56 %), and asthma in 2 (22 %), with an IgE ranging from 213–10,000 IU/ml, suggesting a more severe atopic phenotype [40].

Exact data regarding sensitization patterns are lacking; however, one case report revealed positive reactions on skin prick testing to extracts of *D. pteronyssinus*, cat, dog, white oak, soy, egg, peanut, and corn [30].

Wiskott-Aldrich Syndrome (WAS)

WAS is a severe X-linked immunodeficiency caused by mutations in the gene encoding for WAS protein (WASP), which is an actin regulatory protein that mediates cytoskeletal changes and has been implicated in a variety of cellular functions in both lymphocyte and non-lymphocyte lineages. The classic diagnostic triad includes thrombocytopenia, severe recalcitrant eczema present in 80 % of patients, and immunodeficiency [41]. An early report of 12 patients with Wiskott-Aldrich syndrome described markedly elevated IgE (geometric mean value of 1448 IU/ml) [42]. The authors propose that these high IgE levels reflect chronic antigen stimulation and proliferation of IgE-producing lymphocytes due to failure to eliminate pathogens, and that this IgE is not antigen specific. Further investigation into the pathogenesis of elevated IgE in WAS as well as determining the presence of allergen-specific IgE by skin and serum testing in a cohort of WAS patients is currently in progress.

Inborn Errors of the Toll-Like Receptor and Interleukin-1-Receptor (TIR) Pathway due to Interleukin-1-Receptor-Associated Kinase (IRAK)-4 and Myeloid Differentiation Factor (MyD) 88 Deficiency

IRAK-4 and MyD88 are two proteins involved in toll-like receptor (TLR) signaling; mutations in these proteins lead to clinically related autosomal recessive syndromes characterized by invasive bacterial infections in infancy and early childhood with impaired inflammation. One recent large series evaluated IgE levels in 20 patients with IRAK-4 deficiency, of which 14 (70 %) had increased IgE, ranging from 19–17,400 IU/ml [13]. Of six patients with MyD88 deficiency, 3 (50 %) had elevated IgE, ranging from 53–199 IU/ml. Despite this, no patients in this series reported a history of asthma, and only one reported a history of atopic dermatitis. A variety of allergen-specific IgE was observed in a subset of patients with MyD88 and IRAK-4 deficiencies (personal communication, C. Rodríguez-Gallego).

Immune Dysregulation, Polyendocrinopathy, and Enteropathy, X-Linked (IPEX) and IPEX-Like Syndromes

IPEX is an X-linked condition caused by loss of function mutations in forkhead box protein 3 (FOXP3) leading to decreased numbers and abnormal function of regulatory T (Treg) cells and failure to suppress Th2 inflammation. It causes severe autoimmunity including type I diabetes mellitus, thyroiditis, and protein-losing enteropathy. Moderate to dramatically elevated IgE levels are common, as are food allergies and eczema. One cohort with particularly severe atopic dermatitis, food allergies (milk, peanut), and urticaria but without other autoimmune disease has been described [43]. Although specific data about pattern of sensitization in larger series of patients has not been published, positive serum allergen testing and skin prick tests to food and environmental allergens has been reported [32, 33].

Phosphoglucomutase-3 (PGM3) Deficiency

Patients with mutations in PGM3, a protein component of the glycosylation pathway, were first described in 2014 [16, 44, 45]. Patients have prominent neurologic impairment, skin and lung infections, cutaneous viral infections, and leukocytoclastic vasculitis. Patients have a significant atopic phenotype similar to that seen in DOCK8 deficiency: moderate to severe atopic dermatitis (95 %), asthma (37.5 %), food (54.5 %), drug (37.5 %), and environmental allergies (62.5 %). IgE ranges from normal to very high (up to 140,000 IU/ml); increased serum IgE levels have been proposed to be a result of increased IgE stability caused by aberrant

glycosylation [44]. The allergen specificity of this IgE has not yet been evaluated.

IL-21/IL-21 Receptor Deficiency

Over the past several years, mutations in the IL-21 pathway have been described in eight patients with recurrent sinopulmonary and gastrointestinal infections, including chronic cryptosporidial infections leading to liver disease [9, 10]. All patients in whom IgE was tested were found to have moderate to significant elevations in IgE, with some detectable allergen specific IgE at low titers. Some patients had a history of rhinitis and asthma, but there was no reported history of food allergy or atopic dermatitis despite the elevated IgE (personal communication, Joshua Milner). As IL-21 signals primarily through STAT3 and STAT1, this suggests that a common pathophysiologic mechanism driving IgE production may be present in patients with AD-HIES and IL-21 pathway defects.

Severe Combined Immunodeficiency (SCID) Due to Adenosine Deaminase (ADA) Deficiency

Mutations in ADA lead to severe combined immunodeficiency with profound T-, B-, and natural killer (NK)-cell lymphopenia. Elevated IgE has been described in both early-onset and atypical (hypomorphic) ADA-SCID [2, 46] and is due to restricted T cell receptor (TCR) repertoire. In a cohort of 18 patients with early-onset ADA-SCID, 10 (56 %) were characterized as atopic (median IgE 879 IU/ml), with allergic rhinitis being the most common manifestation. A smaller subset had asthma, food allergies, and mild atopic dermatitis. Sensitization was detected to perennial but not seasonal aeroallergens in 5 of 13 (38 %) patients evaluated by skin or serum allergy testing. Five patients also had sensitization to common food allergens (egg white, milk, peanut, wheat), despite only two reporting clinical history of food allergy.

DiGeorge Syndrome

DiGeorge syndrome is a congenital anomaly typically involving the heart, thymus, and parathyroid glands. Elevated IgE has been noted in atypical complete DiGeorge syndrome, sometimes in association with development of a rash and lymphadenopathy [3, 47]. A questionnaire study of 53 patients with DiGeorge syndrome revealed that 58 % had a history of wheezing (although only 36 % had a diagnosis of asthma), 28 % had eczema, and 21 % had allergic rhinitis [48]. Interestingly, the rate of wheezing and eczema in DiGeorge syndrome patients was over double that in unaffected sibling controls, a finding which has been proposed to be due to Th2 skewing of the T cell compartment in the setting of T cell oligoclonality [15, 49].

Omenn Syndrome (OS)

OS is a phenotypic form of SCID that has been associated with multiple genotypes associated with abnormal or impaired lymphocyte development [50]. Nearly all patients have generalized severe erythroderma and increased IgE levels with eosinophilia. Patients have been shown to have a severely restricted TCR repertoire, likely limiting their ability to generate allergen-specific IgE, although reports of the results of skin prick and serum IgE testing in patients with OS are lacking [51].

Tyrosine Kinase 2 (TYK2) Deficiency

Deficiency in TYK2, a JAK family tyrosine kinase involved in cytokine signaling, is associated with susceptibility to mycobacterial and viral infections. The first described patient with TYK2 deficiency, reported in 2006, had a significantly elevated IgE at 2100 IU/ml with infantile atopic dermatitis but no mention of other atopic disease [52]. However, seven subsequently reported patients with TYK2 deficiency have normal IgE without atopy [53, 54], and attempts to screen cohorts of patients with HIES of unknown genetic cause have not yet revealed further patients with TYK2 deficiency, suggesting that HIES is not typically associated with TYK2 deficiency [55]. As such, further characterization of the atopic sensitization of this cohort has not been pursued.

Conclusions and Future Directions

Immune deficiency and auto-inflammatory/atopic disorders have traditionally been thought of as lying at opposite ends of the spectrum of immunity. In fact, the presence of IgE has been used by some as a marker of an intact humoral immune compartment [56] and elevations of serum IgE generally are accompanied by normal or sometimes increased levels of serum IgG. However, as the disorders highlighted above demonstrate, there is a growing list of humoral, cellular, and combined immune deficiency syndromes that bridge this divide. In fact, a recently published survey of 2263 patients with PIDs registered in the United States Immunodeficiency Network (USIDNET) demonstrated that 1.8 % had self-reported food allergy, and 6 % had atopic dermatitis [57]. This is lower than the prevalence in the general population, however perhaps higher than would be predicted in a cohort of immune deficient patients, many of whom have defects in IgG, IgA, and/or IgM antibody production and thus could be expected to similarly have defects in generating allergen specific IgE.

There are several syndromes characterized by high IgE in which the allergen repertoire has not been described, or for which only very limited data exist. Further investigation into this, as well as the pathways involved in these “overlap

syndromes,” has the potential to shed more light on the genetic pathways involved in the control of IgE production and the development of allergic sensitization. Targeting these pathways could then be explored as a mechanism for the treatment of allergic disease; for example, suppression of the STAT3 pathway via STAT3 inhibitors could be explored in the treatment of mast cell-mediated diseases such as anaphylaxis [22].

Compliance with Ethical Standards

Conflict of Interest Dr. Lawrence has received consulting fees for serving on clinical events committees from Regado Biosciences and Merck & Co.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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